HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2021 June 17.

Published in final edited form as:

Environ Res. 2021 June ; 197: 111086. doi:10.1016/j.envres.2021.111086.

Low-level exposure to lead, mercury, arsenic, and cadmium, and blood pressure among 8-17-year-old participants of the 2009–2016 National Health and Nutrition Examination Survey

Gauri Desai[a,*], **Zhongzheng Niu**[a,1], **Wei Luo**[b], **Seth Frndak**[a], **Amy L. Shaver**[a], **Katarzyna Kordas**[a]

[a]Department of Epidemiology and Environmental Health, University at Buffalo, The State University of New York, USA

[b]Department of Sociology, University at Buffalo, The State University of New York, USA

Abstract

Background: Dysregulation of systolic, diastolic blood pressure (SBP, DBP), and pulse pressure (PP) in children may predict elevated blood pressure (BP) in adulthood. Toxicant exposure is widely studied as a risk factor for high BP in adults, but not in children. We assessed the joint associations between lead (Pb), mercury (Hg), arsenic (As), and cadmium (Cd) exposure and SBP, DBP, and PP among 8–17 year-old participants (n = 1642) of the 2009–2016 National Health and Nutrition Examination Survey (NHANES).

Methods: Participants with at least two BP measures were included. Urinary As and Cd were adjusted for urinary creatinine concentrations. Blood Pb, Hg, and urinary As, Cd were natural log-transformed. Bayesian Kernel Machine Regression (BKMR) analyses were conducted to assess the associations between the toxicant mixture and BP measures. Multivariable regression models assessed the associations between individual toxicants, and the four toxicants simultaneously with each of the outcomes. Interactions with sodium intake were tested.

Results: Exposure to all toxicants was low, with median (5%, 95%) level: Pb, 0.57 (0.26, 1.60) μg/dL; Hg, 0.37 (0.19, 2.12) μg/L; As, 5.61 (1.37, 33.2) μg/g creatinine, Cd, 0.06 (0.03, 0.23) μg/g creatinine. Toxicant mixture showed a statistically significant, inverse association with DBP, but not other BP measures. Linear regressions revealed no association between toxicants, individually

*Corresponding author. gauriabh@buffalo.edu (G. Desai).

[1]Indicates shared first-authorship.

CRediT author statement

Gauri Desai: Methodology, Formal analysis, Writing – original draft. Zhongzheng Niu: Methodology, Formal analysis, Conceptualization, Writing – review & editing. Wei Luo: Methodology, Conceptualization, Writing – review & editing. Seth Frndak: Methodology, Conceptualization, Writing – review & editing. Amy L. Shaver: Methodology, Conceptualization, Writing – review & editing. Katarzyna Kordas: Methodology, Conceptualization, Writing – review & editing.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111086.

“U” indicates urinary toxicants, “B” indicates blood toxicants; SD: standard deviation.

or together, and BP measures. No evidence of interaction of sodium intake with any of the toxicants was observed.

Conclusions: In a nationally representative sample of 8–17 year-olds, we found suggestive inverse association of the mixture of low-level Pb, Hg, As, and Cd, with DBP. Longitudinal studies with multiple toxicants are needed to understand the interactive effects of toxicants on children's BP.

Keywords

Multiple toxicants; Low-level exposure; blood pressure; Children

1. Introduction

Elevated blood pressure (BP) is a known risk factor for multiple cardiovascular diseases. As systolic, diastolic blood pressure, and pulse pressure (SBP, DBP, PP) increase in adults, the risk of death from stroke and heart disease also increases (Rao 2016). Previous studies have shown that PP is highly predictive of cardiovascular disease risk in adults (Mosley et al., 2007). A high PP, i.e., a large difference between SBP and DBP indicates hardening of the arteries or systolic hypertension (Benetoset al., 1998). Hypertension in adults appears to have its origins in childhood. Systolic and, to a lesser extent diastolic, BP track over time, although the tracking is stronger in older and obese children (Chen and Wang 2008; Kagura et al., 2015; Leyvraz et al., 2018). A number of studies have examined secular trends in mean BP and the prevalence of elevated BP in U.S. children and adolescents, all differing on the period of follow-up and the ages of children included (Din-Dzietham et al., 2007; Rosner et al., 2013; Xi et al., 2016; Yang et al., 2016). Based on the 2011–2012 National Health and Nutrition Examination Survey (NHANES), the prevalence of elevated BP among 10–19 year old participants was 1.7% in the U.S.; elevated BP was defined as BP ≥ referent sex-specific, age-specific and height-specific 95th percentile (National Heart 2004; Xi et al., 2016). 1.

Toxicant exposure is increasingly investigated as a risk factor for elevated BP because of the abundant opportunities of exposure through multiple sources, including commonly consumed foods as well as water. For example, for toxicants like cadmium (Cd), arsenic (As), lead (Pb) and mercury (Hg), several foods are well characterized as exposure sources particularly when water toxicant levels are low. Seafood, rice, and rice-based foods are known determinants of urinary arsenic concentrations in the U.S. population (Gilbert-Diamond et al., 2011; Navas-Acien et al., 2011; Signes-Pastor et al., 2016; Signes-Pastor et al., 2018). Other studies based on NHANES data have shown that consumption of breads and cereals, fruit juices, and certain leafy green vegetables are associated with blood or urinary levels of lead, cadmium, and mercury in different age groups (Kim et al., 2019; Desai et al., 2020; Wells et al., 2020).

Studies on toxicant exposure and BP among adults have yielded mixed findings. For example, among Native American participants of the Strong Heart Study, high baseline levels of urinary Cd were associated with faster rates of increase in BP over ten years (Oliver-Williams et al., 2018). On the other hand, a Belgian study found no associations between either urinary or blood Cd levels and BP (Staessenet al., 2000). Studies conducted

in Southeast Asia have indicated a positive correlation between blood Cd levels and both systolic and diastolic BP (Chen et al., 2013; Chen et al., 2015). Arsenic exposure from drinking water was associated with hypertension among adults in Chile and Taiwan, but no association was observed between urinary As and BP among participants of the 2003–2008 NHANES cycles (Chen et al., 1995; Jones et al., 2011; Hall et al., 2017). Low bone and blood Pb levels were associated with elevated BP in studies in Sweden and the U.S. (Hu et al., 1996; Nash et al., 2003; Muntner et al., 2005; Gambelunghe et al., 2016). Among participants of the 2003–2006 NHANES, urinary Hg was associated with lower BP, but blood Hg showed little to no association with hypertension (Park et al., 2013). Fewer studies focus on toxicant exposures and BP among children and adolescents. The handful of studies that have been conducted, seem to indicate that blood levels of both Pb and Cd and urinary concentrations of As may be associated with higher BP in adolescents, while the associations between Hg and BP remain inconsistent (Osorio-Yáñez et al., 2015; Ahn et al., 2018; Chen et al., 2019; Gallego-Vinas et al., 2019; Yao et al., 2020).

Increasingly, studies have begun to examine the effects of multiple exposures, or mixtures, on health outcomes. Even at low levels, toxicants may produce important effects on health outcomes or pathophysiological processes when they occur as a mixture (Kortenkamp et al., 2007). There is currently little understanding of how exposure to multiple toxicants may be related to BP in children and adolescents. A study of the relationship between Pb, Cd, and Hg exposures and BP among 8–17 year-old participants of the 2007–2016 NHANES cycles revealed an inverse association between urinary Cd concentrations and both SBP and DBP, and an inverse association between Hg exposure and SBP, based on multivariable linear and logistic regressions (Yao et al., 2020). The objective of our analysis was to further investigate the association between low-level toxicant exposure and BP among 8–17 year-old participants of the 2009–2016 NHANES cycles by focusing on four toxicants (Pb, Hg, As, and Cd) and carrying out Bayesian Kernel Machine Regression (BKMR) analysis to specifically treat the exposures as a mixture. Our study also includes parallel analysis using multivariable regression methods, and assessing effect modification by sodium intake, a known risk factor for high BP, thereby adding substantially to the previous knowledge base.

2. Methods

2.1. Study design and population

NHANES is a nationally representative, cross-sectional survey conducted by the National Center for Health Statistics (NCHS) for monitoring the health and nutritional status of non-institutionalized individuals in the U.S. The NCHS uses a stratified, multistage probability sampling method to achieve nationally representative samples for each year, and the collected data from questionnaires and laboratory tests are released every two years. Detailed descriptions of the sampling method and data collection are available on the NHANES website (CDC 2009). All procedures that are part of the NHANES have been approved by the National Center for Health Statistics Research Ethics Review Board.

Our study sample consisted of 8–17 year-olds participating in the 2009–2016 NHANES cycles. Of the 6770 participants meeting the criteria for age and survey cycles, those with missing values of blood Pb and Hg levels, urinary As and Cd levels, those who did not have

at least two valid measures of BP taken on the right arm, and those with missing data on age, sex, body mass index (BMI), and sodium intake were excluded, resulting in a complete-case sample of 1642 participants. Previous studies have shown considerable inter-arm variability in BP measures (Cassidy and Jones 2001; Lane et al., 2002), whereas a few others have shown no such variability among healthy individuals (Hashimoto et al., 1984; Eguchi et al., 2007). In face of such inconsistent results and the fact that the populations studied in these studies are varied, we followed the recommendations of the American Academy of Pediatrics' Clinical Practice Guidelines for BP screening and measurement in children and adolescents that state that BP measures should be taken on the right arm (Flynn et al., 2017). Therefore, we excluded participants with BP measures on the left arm and those with no information on the arm of measurement.

2.2. Blood Pb and Hg, and Urinary As and Cd concentrations

Venous whole blood samples were collected by phlebotomists, and were processed at the National Center for Environmental Health. Blood concentrations of Pb and Hg were measured using inductively coupled plasma mass spectrometry (CDC 2016). The limits of detection (LOD) for Pb were 0.25 μg/dL (2009–2012), and 0.07 μg/dL (2013–2016); LOD for Hg were 0.33 μg/L (2009–2010), 0.16 μg/L (2011–2012), and 0.28 μg/L (2013–2016). Values below the LOD were imputed as the LOD divided by the square root of two. There were 0.8%, and 31.1% measures below LOD for Pb, and Hg, respectively.

Concentrations of As and Cd were analyzed in spot urine samples that the participants collected at the time of their appointment in the NHANES mobile examination center; details of the urine collection process are available in the NHANES laboratory manuals (National Health and Nutrition Examination Survey, 2009a,b,c, National Health and Nutrition Examination Survey, 2011a,b,c, National Health and Nutrition Examination Survey, 2013a,b,c, National Health and Nutrition Examination Survey, 2016a,b). Spot urine samples were analyzed for total As concentrations using inductively coupled-plasma dynamic reaction cell-mass spectrometry (Date and Gray 1989; Tanner and Baranov 1999). The LODs for total urinary As were 0.74 μg/L (2009–2010), 1.25 μg/L (2011–2012), and 0.26 μg/L (2013–2016). Urinary Cd concentrations were also assessed from spot urine samples using inductively coupled plasma mass spectrometry (Date and Gray 1989). The LOD for urinary Cd were 0.042 μg/L (2009–2010), 0.056 μg/L (2011–2012), and 0.036 μg/L (2013–2016). Values below the LOD were imputed as the LOD divided by the square root of two. There were 1.2%, and 37.0% measures below LOD for As, and Cd, respectively. Urinary As and Cd concentrations were adjusted for urinary creatinine concentrations to account for the participants' urinary dilution.

2.3. Blood pressure

All NHANES participants ≥8 years of age were eligible for BP measures in the mobile examination centers. Participants were excluded from BP measures if they had any of the following conditions on either arm: rashes, gauze dressings, casts, edema, paralysis, tubes, open sores or wounds, withered arms, arteriovenous shunts, radical mastectomy, or if the BP cuff did not fit on the arm. Participants were asked to rest in a seated position for 5 min, after which three consecutive (30 s apart) readings were obtained using a sphygmomanometer;

BP readings were measured as millimeters of mercury (mmHg). Detailed procedures of BP measurement techniques are available in the NHANES procedure manuals (National Health and Nutrition Examination Survey, 2009a,b,c, National Health and Nutrition Examination Survey, 2011a,b,c, National Health and Nutrition Examination Survey, 2013a,b,c, National Health and Nutrition Examination Survey 2015). Pulse pressure was calculated as the difference between SBP and DBP. The current analysis includes participants with at least two valid BP measures to account for inter personal variability, and because fewer participants had three measures available.

2.4. Covariates

Demographic details of the participants, such as age at enrollment, sex, and race were provided by an adult proxy in an interview. For the present analysis, race was categorized as Non-Hispanic White, Non-Hispanic Black, Hispanic, and other. Socioeconomic status was assessed in terms of poverty to income ratio, and the education of the head of household. Poverty to income ratio was categorized as ≤150%, >150%, or missing. Education of the household head was categorized as <9th grade, 9–11th grade, high school graduate, some college, college or above, or missing. The separate category for missing education data was created to maximize the sample size. Weight and standing height were measured in the mobile examination center; BMI was calculated as weight (kilograms) divided by the square of height (meters) (National Health and Nutrition Examination Survey, 2009a,b,c, National Health and Nutrition Examination Survey, 2011a,b,c, National Health and Nutrition Examination Survey, 2013a,b,c, National Health and Nutrition Examination Survey, 2016a,b). Total energy intake was assessed as kilocalories (kcal) consumed/day based on the first of two 24-h dietary recalls. Fewer participants had completed two 24-h dietary recalls, therefore, data from the first recall was used. Further, the single day recall in NHANES is conducted in a manner to represent the usual average dietary intake in the population (Ahluwalia et al., 2016). Covariates were chosen based on a directed acyclic graph. Sodium intake was treated as an effect modifier because it is a known risk factor for high BP among children and adolescents (Leyvrazet al., 2018). Sodium intake was also assessed based on the first 24-h dietary recall using the US Department of Agriculture’s Food and Nutrient Database for Dietary Studies, and was expressed as mg intake/day.

2.5. Statistical analyses

All analyses were conducted in the complete-case sample of 1642 participants. Descriptive statistics included calculating medians (5th, 95th percentile) and frequencies (%) of sociodemographic and anthropometric characteristics, blood and urinary toxicant concentrations, and BP measures in the study sample as well as among participants who were excluded from the main analyses (n = 5128). Descriptive analyses were first conducted by each survey cycle to understand potential differences in variables by cycle. Because the exposures and outcomes of interest were consistent across all four cycles, data were combined for further analysis.

Blood and urinary toxicant concentrations were natural log-transformed to approximate a normal distribution. Bayesian Kernel Machine Regression (BKMR) models were used to explore the potentially nonlinear, non-additive association of the toxicant mixture with BP

measures. The BKMR is an advanced statistical method emerging in environmental epidemiologic research to handle the complex relationships for high-dimensional vectors of interrelated environmental mixtures with health outcomes (Bobbet al., 2015; Bobb et al., 2018). Briefly, the BKMR model is given by: $Y_i = h(z_{i1}, \ldots, z_{iM}) + \mathbf{x_i}\beta + \varepsilon_i$, where Y_i denotes one of the centered BP measures for individual i ($i = 1, \ldots, n$), z_{iM} is the m^{th} centered, log-transformed toxicant, $h()$ denotes the unknown exposure-response function to be estimated, β represents the effect of the covariates vector $\mathbf{x_i}$, and the residuals $\varepsilon_i \sim N(0, \delta^2)$ are assumed to be independent and identically normally distributed with a common variance. Under the Gaussian kernel machine representation, the exposure-response functions $h()$ are fitted to measure the similarity between individuals' exposure profiles (z_i) regarding their health effects ($h(z_i)$) so that two individuals with similar exposure profiles are closer.

Separate BKMR models were conducted for each of the three BP measures of interest: SBP, DBP, and PP. From the model fitting with 10,000 iterations, summary statistics with confidence intervals were calculated to quantify the overall toxicant mixture effect on each BP measure, as well as each toxicant's single effect on BP while fixing all other toxicants at a certain level (e.g., quartiles). As previously recommended (Bobb et al., 2018), BP measures were compared at different levels of a single toxicant or the toxicant mixture to avoid misleading comparisons in face of non-linear relationships (e.g., a U-shaped relationship). In particular, BP measures were compared at the following levels of a single toxicant or the toxicant mixtures: quartile 3 vs. quartile 1, 50th vs. 20th percentile, and 80th vs. 20th percentile. To examine potential interactive effects of the toxicants on BP measures, the relationship of each toxicant with BP measures was plotted at different quartiles of a second toxicant while fixing the remaining toxicants at their median. Also, each single toxicant's effect on the BP measures was compared at different quartiles of the remaining toxicants.

Ordinary least squares (OLS) linear regression analyses were also conducted to assess the associations between natural log-transformed blood and urinary toxicant concentrations and SBP, DBP, and PP. As a first step, univariate associations of each toxicant and each outcome variable were assessed. Next, covariates (age, sex, race, BMI, total energy intake, NHANES cycle, education of household head, and income to poverty ratio) were added to each model. Subsequently, a covariate-adjusted multiple-toxicant model (blood Pb, Hg, urinary As, Cd) was constructed to assess the association between all four toxicants simultaneously and the endpoints of interest. Interactions by sodium intake were assessed by creating interaction terms between each natural log-transformed toxicant exposure variable and a dichotomous sodium intake variable indicating adequate sodium intake for specific age groups. The cut points reflected the dietary guidelines of Tolerable Upper Intake Levels of 2200 mg/day of sodium for 8–13-year-olds, and 2300 mg/day for 14–17-year-olds (Dietary Guidelines Advisory Committee 2015). Separate interactions by sex were also assessed in exploratory analyses. All interactions were assessed at an alpha level of 0.05, and were adjusted for the same covariates as the main models.

As sensitivity analyses, the linear regression analyses were repeated by excluding participants with urine samples that are considered very dilute (urinary creatinine

concentrations <30 mg/dL; n = 107) or very concentrated (urinary creatinine concentrations >300 mg/dL; n = 41) according to the World Health Organization guidelines for studies of adults with occupational exposures (World Health Organization 1996). However, urinary creatinine concentrations are influenced by several factors such as BMI, muscle mass, dietary intakes, and guidelines meant for occupational studies that primarily include adults may not be directly applicable for studies in children and adolescents. Therefore, participants with creatinine values < 30 mg/dL or >300 mg/dL were not excluded from the main analyses.

All data management, descriptive analyses, and linear regression analyses were conducted in SAS version 9.4. The BKMR analyses were conducted with the *bkmr* package in R 4.0.

3. Results

Supplemental Figure 1 shows the process of arriving at the complete-case sample of 1642 participants. Table 1 presents the sociodemographic and anthropometric characteristics, along with biomarkers of toxicant exposure and BP measures in the study sample (n = 1642) as well as among participants in the 8–17-year-old age group that were excluded from the study (n = 5128). The median (5th, 95th percentile) age of the study participants was 152 (102, 200) months, with approximately equal distribution of both sexes. The median (5th, 95th percentile) levels of blood Pb and Hg, and urinary As and Cd were 0.57 (0.26, 1.60) ug/dL, 0.37 (0.19, 2.12) ug/L, 5.61 (1.37, 33.2) ug/g creatinine, and 0.06 (0.03, 0.23) ug/g creatinine, respectively. The sociodemographic, anthropometric, and biochemical measures of the study participants were comparable to those among participants who were excluded from the study sample.

All toxicants showed a weak to moderate correlation with each other ($0.11 \leq r \leq 0.44$). Figs. 1 and 2 present the results obtained from the BKMR models for SBP and DBP, respectively. As shown in Fig. 1A, As, Cd, and Pb were inversely, whereas Hg was positively correlated with SBP. When the association of each metal with SBP was modeled while holding all other metals at the median, Cd was inversely and statistically associated with SBP (Fig. 1B). Additionally, models of the association between Cd and SBP while fixing the other toxicants at either the 25th, 50th and 75th percentile revealed no effect modification of the Cd – SBP relationship by other toxicants (Fig. 1C). Similarly, there was no indication of effect modification in the association between As, Pb, or Hg and SBP by other metals. As a mixture, the toxicants were inversely associated with SBP, but the association was not statistically significant (Fig. 1D).

All toxicants were weakly but inversely correlated with DBP (Fig. 2A). Fig. 2B presents the relationships between individually modeled toxicants and DBP when the remaining metals are fixed at the median. Arsenic and Pb were not associated whereas Cd was inversely associated with DBP. A cubic curve was observed for the association between Hg and DBP, where DBP was lower at the upper quartile of Hg compared to the lower quartile when other toxicants were fixed at their respective medians. The 95% confidence interval at the highest levels of blood Hg was very wide, indicating very imprecise estimates; no meaningful conclusion can be drawn about how increasing levels of blood Hg relate to DBP. The

association between each of the metals and DBP did not differ when compared at the 25th, 50th, and 75th percentile of the other metals, indicating a lack of interactive effects among the toxicants (Fig. 2C). As a mixture, the toxicants were linearly, inversely, and statistically associated with DBP in the range between 10th and 80th percentile of the mixture levels (Fig. 2D). There were no associations between any single toxicant or the toxicant mixture and PP (Supplemental Figure 2).

Table 2 presents the results of the OLS regressions assessing the associations between toxicant exposure and each measure of BP. No associations were observed in covariate-adjusted single toxicant models, or covariate-adjusted multiple-toxicant models. Results from the sensitivity analyses involving the exclusion of participants with urinary creatinine concentrations <30 mg/dL or >300 mg/dL (Supplemental table 1) were consistent with the main findings.

Table 3 presents the results of the interactions of sodium intake with each toxicant. Of the 892 participants between the ages of 8–13 years, 230 had sodium intake below the Tolerable Upper Intake Levels of 2200 mg/day; 211 of the 750 participants in the 14–17-year age range had intake below the Tolerable Upper Intake Levels of 2300 mg/day. No statistically significant interactions were observed. Supplemental table 2 presents the results of interactions of sex with the toxicant exposures. Higher levels of natural log-transformed blood Pb were associated with higher SBP and PP, but lower DBP among girls. Other toxicants did not show any evidence of interactions with sex.

4. Discussion

In a representative sample of 1642 participants between 8 and 17 years of age from the NHANES 2009–2016 cycles, we found no associations between low-level exposure to Pb, Hg, As, and Cd individually, and measures of BP, i.e., SBP, DBP, or PP. However, we found that the toxicant mixture consisting of low-level urinary As, urinary Cd, blood Pb, and blood Hg showed a statistically significant, inverse association with DBP.

There are few studies that examine the combined effects of multiple toxicants on BP or hypertension in humans, children or adults; therefore, it is difficult to place our findings in the context of published literature. Although one study has previously analyzed the associations between Pb, Hg, and Cd exposure and BP in children from the 2007–2016 NHANES (Yao et al., 2020), several aspects differentiate our study. For example, we included urinary As and investigated potential effect modification by sodium intake and sex. Furthermore, with the use of more advanced analytical methods, our study is the first to examine the mixture effect of toxicants on three measures of BP in children. Given the low level of exposure and the low prevalence of elevated BP in this population-based study, further studies are warranted to replicate our findings.

It is important to consider the mechanistic basis for the observed association between the toxicant mixture and DBP. Oxidative stress is hypothesized to play a role in the pathogenesis of cardiovascular diseases, also influencing blood pressure (Yasunari et al., 2002). Oxidative stress is a well-studied endpoint in relation to blood Pb and urinary As levels among

children, but it is relatively understudied as a mechanistic endpoint of Cd and Hg exposure (Xu et al., 2008; Cuypers et al., 2010; Grotto et al., 2010; Hinhumpatch et al., 2013; Roy and Kordas 2016; Kordas et al., 2018). While most primary pediatric hypertension is determined by genetic predisposition (Oh and Hong 2019), elevated BP in children has been associated with environmental factors such as intrauterine exposure to maternal diabetes (Wright et al., 2009), smoking (Oken et al., 2005), and postnatal formula feeding (Aris et al., 2019). As an environmental insult, exposure to Hg has been less studied in association with BP in children and adolescents. Due to its high affinity for sulfhydryl groups, Hg could induce oxidative stress by suppressing sulfur-containing antioxidants (Valko et al., 2005) and reduce the activity of metalloenzymes (Houston 2011). A result of this process could be the induction of vascular and renal dysfunction and increased risk of hypertension and other cardiovascular diseases. It is possible that these adverse effects of a toxicant mixture are exacerbated in children because of the sensitivity of organ systems to insults during development (McMillen and Robinson 2005).

Studies in young and adult animal models have implicated the nephrotoxicity of Pb in its association with hypertension (Victery 1988). Among human adults, biopsy and renal function studies have indicated that Pb-induced neuropathy is a chronic tubulointerstitial disease that presents with hyperuricemia, gout, and hypertension (Batuman 1993). We found no association between blood levels of Pb and BP in either the BKMR or OLS regression models. The blood Pb concentrations in our study population were low (median: 0.57 μg/dL; 5th, 95th percentile: 0.26, 1.60), well below the current actionable level of 5 μg/dL (Schnur and John 2014). Previously, among adult participants of NHANES 1988–1994, a positive association was observed between blood Pb levels and SBP among African American participants, but not White adults (Vupputuri et al., 2003). African American men had a mean (SE) Pb level of 5.4 (0.2) μg/dL, African American women: 3.4 (0.1) μg/dL, White men: 4.4 (0.1) μg/dL, White women: 3.0 (0.1) μg/dL (Vupputuri et al., 2003); all these levels were higher than in the present study of children. Other studies, also among adults, showed a positive association between blood Pb levels and both SBP and DBP; the mean (SD) blood Pb levels in both these studies were 4.6 (2.6) μg/dL (Schwartz et al., 2000; Glenn et al., 2003). Few studies on blood Pb and BP exist among children, one showing a positive association between blood Pb levels and BP (Jhaveri et al., 1979), and others showing no associations (Selbst et al., 1993; Factor-Litvak et al., 1996). However, these were all conducted among participants with high blood Pb levels (>20 μg/dL), thereby precluding direct comparisons with our study (Jhaveriet al., 1979; Selbst et al., 1993; Factor-Litvak et al., 1996).

The evidence for the association between blood Hg levels and BP has been inconsistent. A study among the Nunavik Inuit adults in Canada showed a positive association between blood Hg levels and SBP, but another study among adults and teenagers in French Polynesia found no associations (Valera, Dewailly et al. 2009, 2011). The mean (95% CI) blood Hg levels were 10.0 μg/L (9.1, 10.8) in the Canadian study, and 8.1 (7.2, 9.1) μg/L among teenagers in French Polynesia (Valera, Dewailly et al. 2009, 2011). Further, among 16–49 year-old women participating in NHANES 1999–2000, no association was seen between blood Hg levels [mean (range): 1.8 (0.1, 21.4) μg/L] and BP (Vupputuriet al., 2005). To our knowledge, no studies on blood Hg levels and BP have been exclusively conducted among

children. Yet, consistent with findings from the studies of low-level Hg exposure in adults, we found no associations between blood Hg levels and BP in OLS regression models. On the other hand, BKMR analyses revealed an association of Hg with DBP that was non-linear, although it was not statistically significant after adjusting for other toxicants. Additional studies with a wide range of Hg exposure levels, as well as its interaction with other toxicants, are needed to better understand the relationship between Hg and BP in children.

The potential association between Cd exposure and increased BP is hypothesized to act via the vascular effects of Cd (Gallagher and Meliker 2010). Cadmium is thought to inhibit endothelial nitric oxide synthase protein in the blood vessels, thus leading to a suppression of acetylcholine-induced vascular relaxation, and eventually hypertension (Yoopanet al., 2008). A systematic review and meta-analysis has suggested a positive association between blood Cd and BP among women; a definitive conclusion, however, cannot be drawn because of the lack of large population-based studies among non-smokers (Gallagher and Meliker 2010). In the current study with 8–17 year-old children, we found no associations between urinary Cd and BP in OLS regression models. However, the BKMR analysis revealed an inverse association of Cd with both SBP and DBP, even after adjusting for other toxicants. Nevertheless, our findings were limited by the fact that ~37% of urinary Cd measures were <LOD. Our findings on Cd exposure and BP need to be confirmed in populations with a wider exposure distribution.

Evidence on the relationship between As exposure and BP among children and adolescents largely comes from geographical areas that are characterized by high levels of groundwater As. For instance, concurrent urinary As concentrations [mean (SD): 158 (207) μg/g creatinine)] were associated with higher SBP among Bangladeshi adolescents between the ages 14–17 years (Chen et al., 2019). In another study in Bangladesh, an increase of 1 mg/L of urinary As concentrations at 18 months of age was associated with 8.2 mmHg (95% CI: 1.37, 15.1) increase in SBP measured at the age of 4.5 years (Hawkesworthet al., 2013). In this study, the median (25%, 75%) urinary As concentrations were 33.9 (18.2, 77.4) μg/L (Hawkesworthet al., 2013). Similar results were seen among 3–8 year-old Mexican children; total urinary As concentrations [mean (range): 59.0 (5.71, 370) ng/ml] were positively associated with both SBP and DBP (Osorio-Ýañez et al., 2015). Urinary As concentrations among participants in our study were substantially lower, median (5th, 95th Percentile) = 5.61 (1.37, 33.2) μg/g creatinine. Our OLS models showed no asociations of As with BP measures, perhaps because the exposure levels were so low.

We observed no statistically significant interactions between sodium intake and biomarkers of any of the toxicants on study endpoints. Sodium intake was positively associated with BP in children and adolescents in observational as well as experimental studies (Leyvrazet al., 2018). Yet no other studies have assessed interactions between this risk factor and low-level toxicant exposure in association with BP in children. Therefore, there is a need to further understand the biological relationships between sodium intake and toxicant exposure among children and adolescents, and to confirm our findings.

Our study findings need to be interpreted in light of certain limitations. First, our analyses are based on cross-sectional data, which do not allow for causal associations to be

established between exposures and outcomes. Second, we did not include smoking or physical activity as covariates in our statistical models, where both these variables could be associated with BP and heavy metal exposure. The decision to exclude these covariates was made to maximize statistical power through maintaining a robust sample size. Although our findings may be explained by the absence of these potential confounders, the likelihood of this is low, given that these variables showed a weak correlation with the exposures and outcomes (all correlation coefficients <0.2). Third, our study participants had low-level toxicant exposure, which limits the generalizability of our findings to populations with similar exposure profiles. Fourth, we made multiple comparisons in both the linear regression models and the BKMR models, increasing the possibility of false positive findings. Fifth, the study relied on BP assessment at a single time point. Finally, although blood markers of Pb and Hg are widely used to assess exposure, they reflect an exposure window of the preceding 2–3 months (Weil et al., 2005; Centers for Disease Control and Prevention 2017), whereas urinary As reflects an exposure window of the preceding few days (NRC 1999). Changes in BP usually occur as a result of chronic processes, therefore, the utility of blood markers of Pb and Hg, and urinary As in relation to BP is limited. On the other hand, to the extent that low or very low-level exposures are likely to track over time in children, the biomarker levels found in our study may be reflective of the children's exposure history.

The strengths of our study include the use of a large, nationally representative sample from four NHANES cycles. Further, we included four toxicants, and assessed their joint associations with BP. We also assessed interactions by sodium intake. The study sample included children with at least 2 BP readings, which reduced the effect of intra-individual variability and measurement error on the observed associations. Our study is among the few assessing the associations between exposure to multiple toxicants at low concentrations and BP in a wide range of ages during childhood and adolescence. Understanding risk factors for BP dysregulation in early life holds public health significance and could be used in the development of interventions.

5. Conclusion

In a nationally representative sample of 8–17 year-old NHANES 2009–2016 participants, we found a suggestive inverse association of low-level exposure to the mixture of Pb, Hg, As, and Cd, with DBP, but not with SBP or PP. Longitudinal studies with multiple toxicants are needed to understand not only the potential interactive effects of toxicants but also possible windows of susceptibility during childhood for developing elevated BP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding sources

Supported in part by Interdisciplinary Training in Cancer Epidemiology: T32CA113951 (Amy Shaver), American Heart Association pre-doctoral fellowship (Zhongzheng Niu, Grant number: 20PRE35120245), and the Community of Excellence in Global Health Equity, University at Buffalo (Seth Frndak & Gauri Desai).

Abbreviations:

BKMR	Bayesian Kernel Machine Regression
BP	Blood pressure
BMI	Body mass index
DBP	Diastolic blood pressure
LOD	Limit of detection
NHANES	National Health and Nutrition Examination Survey
OLS	Ordinary least squares
PP	Pulse pressure
SBP	Systolic blood pressure

References

Ahluwalia N, Dwyer J, Terry A, Moshfegh A, Johnson C, 2016. Update on NHANES dietary data: focus on collection, release, analytical considerations, and uses to inform public policy. Advances in Nutrition 7 (1), 121–134. [PubMed: 26773020]

Ahn J, Kim NS, Lee BK, Park J, Kim Y, 2018. Association of blood pressure with blood lead and cadmium levels in Korean adolescents: analysis of data from the 2010–2016 Korean national health and nutrition examination survey. J. Kor. Med. Sci 33 (44), e278.

Aris IM, Rifas-Shiman SL, Li LJ, Belfort MB, Hivert MF, Oken E, 2019. Early-life predictors of systolic blood pressure trajectories from infancy to adolescence: findings from project viva. Am. J. Epidemiol 188 (11), 1913–1922. [PubMed: 31497850]

Batuman V, 1993. Lead nephropathy, gout, and hypertension. Am. J. Med. Sci 305 (4), 241–247. [PubMed: 8475950]

Benetos A, Rudnichi A, Safar M, Guize L, 1998. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 32 (3), 560–564. [PubMed: 9740626]

Bobb JF, Henn BC, Valeri L, Coull BA, 2018. Statistical software for analyzing the health effects of multiple concurrent exposures via Bayesian kernel machine regression. Environ. Health 17 (1), 1–10. [PubMed: 29301538]

Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M, Godleski JJ, Coull BA, 2015. Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16 (3), 493–508. [PubMed: 25532525]

Cassidy P, Jones K, 2001. A study of inter-arm blood pressure differences in primary care. J. Hum. Hypertens 15 (8), 519–522. [PubMed: 11494088]

CDC, 2009. Overview of NHANES Survey Design and Weights. Centers for Disease Control, Atlanta, Ga.

CDC, 2016. MEC Laboratory Procedures.

Centers for Disease Control and Prevention, C, 2017. Biomonitoring summary - lead. https://www.cdc.gov/biomonitoring/Lead_BiomonitoringSummary.html#:~:text=Lead%20is%20cleared%20from%20the,life%20of%20years%20to%20decades. (Accessed 13 July 2020).

Chen C-J, Hsueh Y-M, Lai M-S, Shyu M-P, Chen S-Y, Wu M-M, Kuo T-L, Tai T-Y, 1995. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25 (1), 53–60. [PubMed: 7843753]

Chen X, Wang Y, 2008. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 117 (25), 3171. [PubMed: 18559702]

Chen X, Wang Z, Zhu G, Liang Y, Jin T, 2015. Benchmark dose estimation of cadmium reference level for hypertension in a Chinese population. Environ. Toxicol. Pharmacol 39 (1), 208–212. [PubMed: 25528411]

Chen X, Zhu G, Lei L, Jin T, 2013. The association between blood pressure and blood cadmium in a Chinese population living in cadmium polluted area. Environ. Toxicol. Pharmacol 36 (2), 595–599. [PubMed: 23834962]

Chen Y, Wu F, Liu X, Parvez F, LoIacono NJ, Gibson EA, Kioumourtzoglou M-A, Levy D, Shahriar H, Uddin MN, 2019. Early life and adolescent arsenic exposure from drinking water and blood pressure in adolescence. Environ. Res 178, 108681. [PubMed: 31520830]

Cuypers A, Plusquin M, Remans T, Jozefczak M, Keunen E, Gielen H, Opdenakker K, Nair AR, Munters E, Artois TJ, 2010. Cadmium stress: an oxidative challenge. Biometals 23 (5), 927–940. [PubMed: 20361350]

Date AR, Gray AL, 1989. Applications of Inductively Coupled Plasma Mass Spectrometry.

Desai G, Anzman-Frasca S, Vernarelli JA, Ravenscroft J, Yang J, Burstein G, Kordas K, 2020. Examining Links between Diet and Lead Exposure in Young Children: 2009–2014 National Health and Nutrition Examination Survey. Academic Pediatrics In Press.

Dietary Guidelines Advisory Committee, D., 2015. Dietary Guidelines for Americans 2015–2020. Government Printing Office.

Din-Dzietham R, Liu Y, Bielo M-V, Shamsa F, 2007. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. Circulation 116 (13), 1488–1496. [PubMed: 17846287]

Eguchi K, Yacoub M, Jhalani J, Gerin W, Schwartz JE, Pickering TG, 2007. Consistency of blood pressure differences between the left and right arms. Arch. Intern. Med 167 (4), 388–393. [PubMed: 17325301]

Factor-Litvak P, Kline JK, Popovac D, Hadzialijevic S, Lekic V, Preteni-Rexhepi E, Capuni-Paracka S, Slavkovich V, Graziano J, 1996. Blood lead and blood pressure in young children. Epidemiology 633–637. [PubMed: 8899391]

Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM, 2017. Clinical Practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 140 (3).

Gallagher CM, Meliker JR, 2010. Blood and urine cadmium, blood pressure, and hypertension: a systematic review and meta-analysis. Environ. Health Perspect 118 (12), 1676–1684. [PubMed: 20716508]

Gallego-Vinas G, Ballester F, Llop S, 2019. Chronic mercury exposure and blood pressure in children and adolescents: a systematic review. Environ. Sci. Pollut. Res. Int 26 (3), 2238–2252. [PubMed: 30519915]

Gambelunghe A, Sallsten G, Borńe Y, Forsgard N, Hedblad B, Nilsson P, Fagerberg B, Engström G, Barregard L, 2016. Low-level exposure to lead, blood pressure, and hypertension in a population-based cohort. Environ. Res 149, 157–163. [PubMed: 27208466]

Gilbert-Diamond D, Cottingham KL, Gruber JF, Punshon T, Sayarath V, Gandolfi AJ, Baker ER, Jackson BP, Folt CL, Karagas MR, 2011. Rice consumption contributes to arsenic exposure in US women. Proc. Natl. Acad. Sci. Unit. States Am 108 (51), 20656–20660.

Glenn BS, Stewart WF, Links JM, Todd AC, Schwartz BS, 2003. The longitudinal association of lead with blood pressure. Epidemiology 30–36. [PubMed: 12500043]

Grotto D, Valentini J, Fillion M, Passos CJS, Garcia SC, Mergler D, Barbosa F Jr., 2010. Mercury exposure and oxidative stress in communities of the Brazilian Amazon. Sci. Total Environ 408 (4), 806–811. [PubMed: 19914681]

Hall EM, Acevedo J, López FG, Cortés S, Ferreccio C, Smith AH, Steinmaus CM, 2017. Hypertension among adults exposed to drinking water arsenic in Northern Chile. Environ. Res 153, 99–105. [PubMed: 27918984]

Hashimoto F, Hunt WC, Hardy L, 1984. Differences between right and left arm blood pressures in the elderly. West. J. Med 141 (2), 189. [PubMed: 6495723]

Hawkesworth S, Wagatsuma Y, Kippler M, Fulford AJ, Arifeen SE, Persson LA, Moore SE, Vahter M, 2013. Early exposure to toxic metals has a limited effect on blood pressure or kidney function in later childhood, rural Bangladesh. Int. J. Epidemiol 42 (1), 176–185. [PubMed: 23243118]

Hinhumpatch P, Navasumrit P, Chaisatra K, Promvijit J, Mahidol C, Ruchirawat M, 2013. Oxidative DNA damage and repair in children exposed to low levels of arsenic in utero and during early childhood: application of salivary and urinary biomarkers. Toxicol. Appl. Pharmacol 273 (3), 569–579. [PubMed: 24128852]

Houston MC, 2011. Role of mercury toxicity in hypertension, cardiovascular disease, and stroke. J. Clin. Hypertens 13 (8), 621–627.

Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A, 1996. The relationship of bone and blood lead to hypertension: the Normative Aging Study. J. Am. Med. Assoc 275 (15), 1171–1176.

Jhaveri RC, Lavorgna L, Dube SK, Glass L, Khan F, Evans HE, 1979. Relationship of blood pressure to blood lead concentrations in small children. Pediatrics 63 (4), 674–676. [PubMed: 440885]

Jones MR, Tellez-Plaza M, Sharrett AR, Guallar E, Navas-Acien A, 2011. Urine arsenic and hypertension in US adults: the 2003–2008 NHANES. Epidemiology (Cambridge, Mass 22 (2), 153.

Kagura J, Adair LS, Musa MG, Pettifor JM, Norris SA, 2015. Blood pressure tracking in urban black South African children: birth to twenty cohort. BMC Pediatr. 15 (1), 78. [PubMed: 26173634]

Kim K, Melough MM, Vance TM, Noh H, Koo SI, Chun OK, 2019. Dietary cadmium intake and sources in the US. Nutrients 11 (1), 2.

Kordas K, Roy A, Vahter M, Ravenscroft J, Mañay N, Peregalli F, Martínez G, Queirolo EI, 2018. Multiple-metal exposure, diet, and oxidative stress in Uruguayan school children. Environ. Res 166, 507–515. [PubMed: 29957504]

Kortenkamp A, Faust M, Scholze M, Backhaus T, 2007. Low-level exposure to multiple chemicals: reason for human health concerns? Environ. Health Perspect 115 (Suppl. 1), 106–114. [PubMed: 18174958]

Lane D, Beevers M, Barnes N, Bourne J, John A, Malins S, Beevers DG, 2002. Inter-arm differences in blood pressure: when are they clinically significant? J. Hypertens 20 (6), 1089–1095. [PubMed: 12023677]

Leyvraz M, Chatelan A, da Costa BR, Taffe P, Paradis G, Bovet P, Bochud M, Chiolero A, 2018a. Sodium intake and blood pressure in children and adolescents: a systematic review and meta-analysis of experimental and observational studies. Int. J. Epidemiol 47 (6), 1796–1810. [PubMed: 29955869]

Leyvraz M, Wahlen R, Bloetzer C, Paradis G, Bovet P, Chiolero A, 2018b. Persistence of elevated blood pressure during childhood and adolescence: a school-based multiple cohorts study. J. Hypertens 36 (6), 1306–1310. [PubMed: 29517559]

McMillen IC, Robinson JS, 2005. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol. Rev 85 (2), 571–633. [PubMed: 15788706]

Mosley WJ, Greenland P, D.B., Lloyd-Jones DM, 2007. Predictive utility of pulse pressure and other blood pressure measures for cardiovascular outcomes. Hypertension 49 (6), 1256–1264. [PubMed: 17420336]

Muntner P, Menke A, DeSalvo KB, Rabito FA, Batuman V, 2005. Continued decline in blood lead levels among adults in the United States: the National Health and Nutrition Examination Surveys. Arch. Intern. Med 165 (18), 2155–2161. [PubMed: 16217007]

Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, Silbergeld EK, 2003. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. J. Am. Med. Assoc 289 (12), 1523–1532.

National Health and Nutrition Examination Survey, N, 2009a. Anthropometry Procedures Manual.

National Health and Nutrition Examination Survey, N, 2009b. Health Tech/Blood Pressure Procedures Manual.

National Health and Nutrition Examination Survey, N, 2009c. MEC Laboratory Procedures Manual.

National Health and Nutrition Examination Survey, N, 2011a. Anthropometry Procedures Manual.

National Health and Nutrition Examination Survey, N, 2011b. MEC Laboratory Procedures Manual.

National Health and Nutrition Examination Survey, n, 2011c. Physician Examination Procedures Manual.

National Health and Nutrition Examination Survey, N, 2013a. Anthropometry Procedures Manual.

National Health and Nutrition Examination Survey, N, 2013b. MEC Laboratory Procedures Manual.

National Health and Nutrition Examination Survey, N, 2013c. Physician Examination Procedures Manual.

National Health and Nutrition Examination Survey, N, 2015. Physician Examination Procedures Manual.

National Health and Nutrition Examination Survey, N, 2016a. Anthropometry Procedures Manual.

National Health and Nutrition Examination Survey, N, 2016b. MEC Laboratory Procedures Manual.

National Heart, L., Blood Institute, N.H.L.B., 2004. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114 (2 Suppl. 4th Report), 555–576. [PubMed: 15286277]

Navas-Acien A, Francesconi KA, Silbergeld EK, Guallar E, 2011. Seafood intake and urine concentrations of total arsenic, dimethylarsinate and arsenobetaine in the US population. Environ. Res 111 (1), 110–118. [PubMed: 21093857]

NRC, N.R.C., 1999. Arsenic in Drinking Water. National Academies Press.

Oh JH, Hong YM, 2019. Blood pressure trajectories from childhood to adolescence in pediatric hypertension. Korean Circulation Journal 49 (3), 223–237. [PubMed: 30808073]

Oken E, Huh SY, Taveras EM, Rich-Edwards JW, Gillman MW, 2005. Associations of maternal prenatal smoking with child adiposity and blood pressure. Obes. Res 13 (11), 2021–2028. [PubMed: 16339135]

Oliver-Williams C, Howard AG, Navas-Acien A, Howard BV, Tellez-Plaza M, Franceschini N, 2018. Cadmium body burden, hypertension, and changes in blood pressure over time: results from a prospective cohort study in American Indians. Journal of the American Society of Hypertension 12 (6), 426–437. [PubMed: 29605538]

Osorio-Yáñez C, Ayllon-Vergara JC, Arreola-Mendoza L, Aguilar-Madrid G, Hernández-Castellanos E, Sanchez-Peña LC, Del Razo LM, 2015. Blood pressure, left ventricular geometry, and systolic function in children exposed to inorganic arsenic. Environ. Health Perspect 123 (6), 629–635. [PubMed: 25738397]

Park SK, Lee S, Basu N, Franzblau A, 2013. Associations of blood and urinary mercury with hypertension in US adults: the NHANES 2003–2006. Environ. Res 123, 25–32. [PubMed: 23472608]

Rao G, 2016. Diagnosis, Epidemiology, and management of hypertension in children. Pediatrics 138 (2), e20153616. [PubMed: 27405770]

Rosner B, Cook NR, Daniels S, Falkner B, 2013. Childhood blood pressure trends and risk factors for high blood pressure: the NHANES experience 1988–2008. Hypertension 62 (2), 247–254. [PubMed: 23856492]

Roy A, Kordas K, 2016. The relation between low-level lead exposure and oxidative stress: a review of the epidemiological evidence in children and non-occupationally exposed adults. Current Environmental Health Reports 3 (4), 478–492. [PubMed: 27726071]

Schnur J, John RM, 2014. Childhood lead poisoning and the new Centers for Disease Control and Prevention guidelines for lead exposure. Journal of the American Association of Nurse Practitioners 26 (5), 238–247. [PubMed: 24616453]

Schwartz BS, Stewart WF, Todd AC, Simon D, Links JM, 2000. Different associations of blood lead, meso 2, 3-dimercaptosuccinic acid (DMSA)-chelatable lead, and tibial lead levels with blood pressure in 543 former organolead manufacturing workers. Arch. Environ. Health 55 (2), 85–92. [PubMed: 10821507]

Selbst SM, Sokas RK, Henretig FM, Weller SC, Tershakovec AM, 1993. The effect of blood lead on blood pressure in children. J. Environ. Pathol. Toxicol. Oncol 12 (4), 213–218. [PubMed: 8189378]

Signes-Pastor AJ, Carey M, Meharg AA, 2016. Inorganic arsenic in rice-based products for infants and young children. Food Chem. 191, 128–134. [PubMed: 26258711]

Signes-Pastor AJ, Cottingham KL, Carey M, Sayarath V, Palys T, Meharg AA, Folt CL, Karagas MR, 2018. Infants' dietary arsenic exposure during transition to solid food. Sci. Rep 8 (1), 1–8. [PubMed: 29311619]

Staessen JA, Kuznetsova T, Roels HA, Emelianov D, Fagard R, 2000. Exposure to cadmium and conventional and ambulatory blood pressures in a prospective population study. Am. J. Hypertens 13 (2), 146–156. [PubMed: 10701814]

Tanner SD, Baranov VI, 1999. Theory, design, and operation of a dynamic reaction cell for ICP-MS. Atom. Spectros 20, 45–52.

Valera B, Dewailly E, Poirier P, 2009. Environmental mercury exposure and blood pressure among Nunavik Inuit adults. Hypertension 54 (5), 981–986. [PubMed: 19805642]

Valera B, Dewailly É, Poirier P, Counil E, Suhas E, 2011. Influence of mercury exposure on blood pressure, resting heart rate and heart rate variability in French Polynesians: a cross-sectional study. Environ. Health 10 (1), 99. [PubMed: 22078280]

Valko M, Morris H, Cronin MT, 2005. Metals, toxicity and oxidative stress. Curr. Med. Chem 12 (10), 1161–1208. [PubMed: 15892631]

Victery W, 1988. Evidence for effects of chronic lead exposure on blood pressure in experimental animals: an overview. Environ. Health Perspect 78, 71–76. [PubMed: 3060353]

Vupputuri S, He J, Muntner P, Bazzano Lydia A, Whelton Paul K, Batuman V, 2003. Blood lead level is associated with elevated blood pressure in blacks. Hypertension 41 (3), 463–468. [PubMed: 12623944]

Vupputuri S, Longnecker MP, Daniels JL, Guo X, Sandler DP, 2005. Blood mercury level and blood pressure among US women: results from the National Health and Nutrition Examination Survey 1999–2000. Environ. Res 97 (2), 195–200. [PubMed: 15533335]

Weil M, Bressler J, Parsons P, Bolla K, Glass T, Schwartz B, 2005. Blood mercury levels and neurobehavioral function. J. Am. Med. Assoc 293 (15), 1875–1882.

Wells EM, Kopylev L, Nachman R, Radke EG, Segal D, 2020. Seafood, wine, rice, vegetables, and other food items associated with mercury biomarkers among seafood and non-seafood consumers: NHANES 2011–2012. J. Expo. Sci. Environ. Epidemiol 30 (3), 504–514. [PubMed: 32015433]

World Health Organization, W., 1996. Biological Monitoring of Chemical Exposure in the Workplace: Guidelines. World Health Organization.

Wright CS, Rifas-Shiman SL, Rich-Edwards JW, Taveras EM, Gillman MW, Oken E, 2009. Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure. Am. J. Hypertens 22 (2), 215–220. [PubMed: 19023272]

Xi B, Bovet P, Hong YM, Chiolero A, Kim HS, Zhang T, Zhao M, 2016. Recent blood pressure trends in adolescents from China, Korea, Seychelles and the United States of America, 1997–2012. J. Hypertens 34 (10), 1948–1958. [PubMed: 27467766]

Xu Y, Wang Y, Zheng Q, Li X, Li B, Jin Y, Sun X, Sun G, 2008. Association of oxidative stress with arsenic methylation in chronic arsenic-exposed children and adults. Toxicol. Appl. Pharmacol 232 (1), 142–149. [PubMed: 18640141]

Yang Q, Zhong Y, Merritt R, Cogswell ME, 2016. Trends in high blood pressure among United States adolescents across body weight category between 1988 and 2012. J. Pediatr 169, 166–173. [PubMed: 26563532]

Yao B, Lu X, Xu L, Wang Y, Qu H, Zhou H, 2020. Relationship between low-level lead, cadmium and mercury exposures and blood pressure in children and adolescents aged 8–17 years: an exposure-response analysis of NHANES 2007–2016. Science of The Total Environment, p. 138446.

Yasunari K, Maeda K, Nakamura M, Yoshikawa J, 2002. Oxidative stress in leukocytes is a possible link between blood pressure, blood glucose, and C-reacting protein. Hypertension 39 (3), 777–780. [PubMed: 11897762]

Yoopan N, Watcharasit P, Wongsawatkul O, Piyachaturawat P, Satayavivad J, 2008. Attenuation of eNOS expression in cadmium-induced hypertensive rats. Toxicol. Lett 176 (2), 157–161. [PubMed: 18155860]

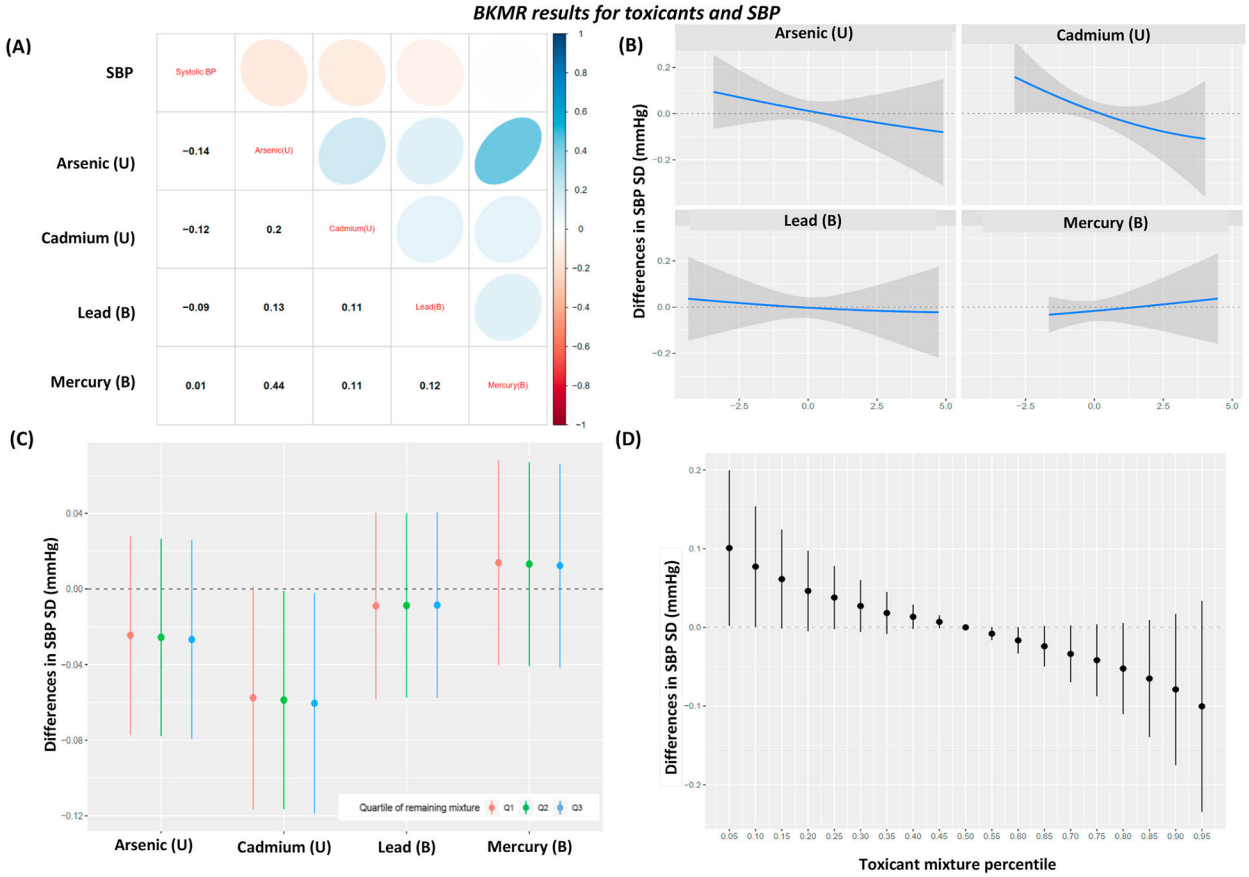

Fig. 1.

Association of toxicants with SBP estimated by Bayesian Kernel Machine Regression (BKMR) among 1642 children aged 8–17 years from NHANES 2009–2016. Model adjusted for age, sex, race, BMI, total energy intake, NHANES cycle, education of household head, and income to poverty ratio. (**A**) Pearson correlation matrix for SBP and toxicants. (**B**) Univariate exposure-response function and 95% confidence bands for each toxicant with the other toxicants fixed at the median. (**C**) Single toxicant effect on SBP comparing the upper quartile to the lower quartile level of a particular toxicant while fixing the other toxicants at the 25th, 50th, and 75th percentile. (**D**) Toxicant mixture effect on SBP, comparing various percentiles of the mixture to the median (50th percentile).

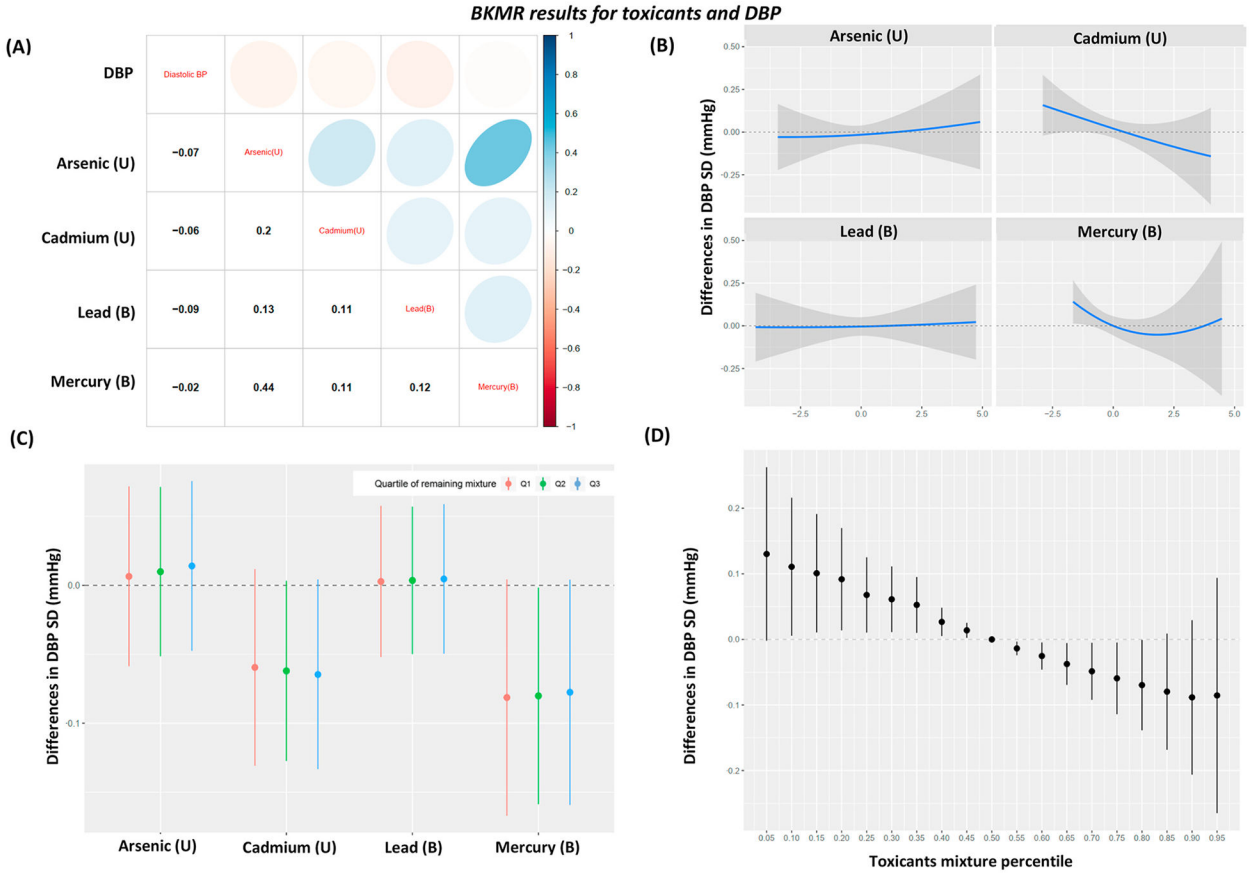

Fig. 2.

Association of toxicants with DBP estimated by Bayesian Kernel Machine Regression (BKMR) among 1642 children aged 8–17 years from NHANES 2009–2016. Model adjusted for age, sex, race, BMI, total energy intake, NHANES cycle, education of household head, and income to poverty ratio. (**A**) Pearson correlation matrix for DBP and toxicants. (**B**) Univariate exposure-response function and 95% confidence bands for each toxicant with the other toxicants fixed at the median. (**C**) Single toxicant effect on DBP comparing the upper quartile to the lower quartile level of a particular toxicant while fixing the other toxicants at the 25th, 50th, and 75th percentile. (**D**) Toxicant mixture effect on DBP, comparing various percentiles of the mixture to the median (50th percentile). “U” indicates urinary toxicants, “B” indicates blood toxicants; SD: standard deviation.

Table 1

Sociodemographic, anthropometric, and biochemical characteristics of 8–17 year-old 2009–2016 NHANES participants who were included in (n = 1642) vs. excluded (n = 5, 128) from the analyses.

Participant Characteristics	Included in Study Sample (n = 1642)	Variable-specific sample size among those excluded from the study	Total excluded from Study Sample (n = 5128)
Age, months, median (5th, 95th Percentile)	152 (102, 200)	5128	143 (100, 198)
Sex, n (%)			
Males	818 (49.8)	5128	2621 (51.1)
Females	824 (50.2)		2507 (48.9)
Race, n (%)			
Non-Hispanic White	435 (26.5)	5128	1429 (27.9)
Non-Hispanic Black	379 (23.1)		1263 (24.6)
Hispanic	599 (36.5)		1727 (33.7)
Other	229 (13.9)		709 (13.8)
Poverty to Income Ratio, n (%)		5128	
≤150%	749 (45.6)		2322 (45.3)
>150%	780 (47.5)		2399 (46.8)
Missing	113 (6.9)		407 (7.9)
Education of Household Head, n (%)	172 (10.5)		
Less Than 9th Grade	279 (17.0)	5128	582 (11.4)
9–11th Grade	332 (20.2)		732 (14.3)
High School Graduate	458 (27.9)		1115 (21.7)
Some College	354 (21.5)		1443 (28.1)
College or above	47 (2.90)		1090 (21.3)
Missing			166 (3.2)
Body Mass Index (kg/m^2), median (5th, 95th Percentile)	20.4 (15.1, 33.6)	5083	20.1 (14.8, 32.2)
Blood Pb (μg/dL), median (5th, 95th Percentile)	0.57 (0.26, 1.60)	5128	0.44 (0.05, 1.57)
Blood Hg (μg/L), median (5th, 95th Percentile)	0.37 (0.19, 2.12)	5128	0.23 (0.11, 1.52)
Urinary As (μg/g creatinine), median (5th, 95th Percentile)	5.61 (1.37, 33.2)	4910	0.39 (0.08, 7.09)
Urinary Cd (μg/g creatinine), median (5th, 95th Percentile)	0.06 (0.03, 0.23)	4910	0.03 (0.01, 0.13)
Urinary creatinine (mg/dL), median (5th, 95th Percentile)	107 (26.0, 260)	4910	111 (27.0, 264)
Systolic Blood Pressure (mmHg), median (5th, 95th Percentile)	105 (89.3, 122)	4707	104 (89.3, 121)
Diastolic Blood Pressure (mmHg), median (5th, 95th Percentile)	56.7 (38.0, 73.3)	4693	560. (28.0, 72.7)
Pulse Pressure (mmHg), median (5th, 95th Percentile)	47.3 (28.7, 71.0)	4693	48.7 (30.0, 79.3)

Units: μg/dL: Micrograms per deciliter, μg/L: Micrograms per liter, mmHg: Millimeters of mercury.

Chemical Symbols, alphabetical: As: Arsenic, Cd: Cadmium, Hg: Mercury, Pb: Lead.

Table 2

OLS[1] linear regression results showing the associations between toxicant exposure and systolic, diastolic, and pulse pressure among study participants (n = 1642).

	SBP, mmHg β (95% CI)	DBP, mmHg β (95% CI)	PP, mmHg β (95% CI)
Univariate Single Toxicant Models			
Log Blood Pb (μg/dL)	**−1.48 (−2.31, −0.65)**	**−1.64 (−2.56, −0.73)**	− 0.17 (−0.94, 1.27)
Log Blood Hg (μg/L)	0.06 (−0.54, 0.66)	− 0.26 (−0.92, 0.40)	0.32 (−0.47, 1.11)
Log Urinary As (μg/g creatinine)	**−1.65 (−2.23, −1.07)**	**−0.91 (−1.55, −0.26)**	− 0.75 (−1.52, 0.03)
Log Urinary Cd (μg/g creatinine)	**−1.82 (−2.55, −1.09)**	**−0.97 (−1.78−0.16)**	− 0.85 (−1.82, 0.12)
Covariate-Adjusted Single Toxicant Models[a]			
Log Blood Pb (μg/dL)	− 0.27 (−1.07, 0.53)	− 0.06 (−1.05, 0.93)	− 0.21 (−1.39, 0.98)
Log Blood Hg (μg/L)	0.005 (−0.53, 0.54)	− 0.59 (−1.25, 0.07)	0.59 (−0.19, 1.38)
Log Urinary As (μg/g creatinine)	− 0.32 (−0.84, 0.21)	− 0.20 (−0.86, 0.45)	− 0.11 (−0.89, 0.67)
Log Urinary Cd (μg/g creatinine)	− 0.59 (−1.25, 0.08)	− 0.76 (−1.58, 0.06)	0.17 (−0.81, 1.15)
Covariate-Adjusted Multiple-Toxicant Models[b]			
Log Blood Pb (μg/dL)	− 0.23 (−1.05, 0.58)	0.11 (−0.89, 1.11)	− 0.34 (−1.54, 0.86)
Log Blood Hg (μg/L)	0.20 (−0.40, 0.80)	− 0.63 (−1.37, 0.11)	0.83 (−0.05, 1.72)
Log Urinary As (μg/g creatinine)	− 0.33 (−0.92, 0.27)	0.15 (−0.58, 0.88)	− 0.48 (−1.35, 0.40)
Log Urinary Cd (μg/g creatinine)	− 0.53 (−1.20, 0.14)	− 0.74 (−1.57, 0.09)	0.21 (−0.78, 1.21)

[1] Ordinary least squares.

Units: μg/dL – Micrograms per deciliter; μg/g – Micrograms per gram, μg/L – Micrograms per liter, mmHg: Millimeters of mercury.

Chemical Symbols and Abbreviations, alphabetical: As – Arsenic; Cd – Cadmium; DBP – Diastolic blood pressure, Hg – Mercury; Pb – Lead; PP – Pulse pressure, SBP – Systolic blood pressure.

Bolded values indicate statistical significance at an alpha level of 0.05. “Log” refers to natural log-transformation Urinary As and Cd were adjusted for urinary creatinine prior to natural log-transformation.

[a] Adjusted for age, sex, race, BMI, total energy intake, NHANES cycle, education of household head, and income to poverty ratio. Each metal predicts blood pressure outcome separately.

[b] Adjusted for the same covariates; all metals are included together in the same model.

Table 3

Interaction between sodium intake[a] and toxicant exposure among study participants (n= 1642).

	SBP, mmHg β (95% CI)	DBP, mmHg β (95% CI)	PP, mmHg β (95% CI)
Covariate Adjusted Single Toxicant Models with Interaction terms[b]			
Log Blood Pb[a] Na intake	−0.84 (−2.48, 0.81)	1.69 (−0.34, 3.72)	1.68 (−0.48, 3.84)
Log Blood Hg[a] Na intake	0.01 (−1.16, 1.19)	0.24 (−1.21, 1.69)	−0.23 (−1.96, 1.51)
Log Urinary As[a] Na intake	−0.38 (−1.54, 0.78)	1.00 (−0.43, 2.43)	−1.38 (−3.10, 0.33)
Log Urinary Cd[a] Na intake	−1.21 (−2.65, 0.23)	0.39 (−1.39, 2.17)	−1.60 (−3.73, 0.53)

Units: mmHg: Millimeters of mercury.

Chemical Symbols and Abbreviations, alphabetical: As – Arsenic; Cd – Cadmium; DBP – Diastolic blood pressure, Hg – Mercury; Na – Sodium; Pb – Lead; PP – Pulse pressure; SBP – Systolic blood pressure.

Bolded values indicate statistical significance at an alpha level of 0.05. “Log” refers to natural log-transformation Urinary As and Cd were adjusted for urinary creatinine prior to natural log-transformation.

[a]Sodium intake dichotomized as ≤2200 mg/day, n = 230 vs. >2200 mg/day, n = 662 for participants between 8 and 13 years of age, and as ≤2300 mg/day, n = 211 vs. >2300 mg/day, n = 539 for participants between 14 and 17 years of age.

[b]Adjusted for age, sex, race, BMI, total energy intake, NHANES cycle, education of household head, and income to poverty ratio. Each metal predicts blood pressure outcome separately.