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The Association between Blood Metals and Hypertension in the GuLF Study

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Abstract

Background—Both essential and non-essential metals come from natural and anthropogenic sources. Metals can bioaccumulate in humans and may impact human health, including hypertension.

Methods—Blood metal (cadmium, lead, mercury, manganese, and selenium) concentrations were measured at baseline for a sample of participants in the Gulf Long-Term Follow-up (GuLF) Study. The GuLF Study is a prospective cohort study focused on potential health effects following the 2010 *Deepwater Horizon* oil spill. Hypertension was defined as high systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure or taking anti-hypertensive medications. A total of 957 participants who had blood measurement for at least one metal, baseline blood pressure measurements, information on any anti-hypertensive medication use, and relevant covariates were included in this cross-sectional analysis. We used Poisson regression to explore the association between individual blood metal levels and hypertension. Quantile-based g-computation was used to investigate the association between the metal mixture and hypertension. We also explored the association between individual blood metal levels and continuous blood pressure measurements using general liner regression.

Results—Comparing the highest quartile of blood metals with the lowest (Q4vs1), the hypertension prevalence ratio (PR) was 0.92 (95% confidence interval (CI)=0.73,1.15) for cadmium, 0.86 (95%CI=0.66,1.12) for lead, 0.89 (95%CI=0.71,1.12) for mercury, 1.00

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(95%CI=0.80,1.26) for selenium, and 1.22 (95%CI=0.95,1.57) for manganese. We observed some qualitative differences across race and BMI strata although none of these differences were statistically significant. In stratified analyses, the PR(Q4vs1) for mercury was 0.69 (95%CI=0.53, 0.91) in White participants and 1.29 (95%CI=0.86,1.92) in Black participants (p for interaction=0.5). The PR(Q4vs1) for manganese was relatively higher in Black participants (PR=1.37, 95%CI=0.92,2.05) than in White participants (PR=1.15, 95%CI=0.83,1.60, p for interaction=0.5), with a suggestive dose-response among Blacks. After stratifying by obesity (BMI≥30 and <30), positive associations of cadmium (PR[Q4vs1]=1.19, 95%CI=0.91,1.56, p for interaction=0.5), lead (PR[Q4vs1]=1.14, 95%CI=0.84,1.55, p for interaction=1.0) and manganese (PR=1.25, 95%CI=0.93,1.68, p for interaction=0.8) with hypertension were observed in participants with BMI≥30, but not in participants with BMI<30. The joint effect of the metal mixture was 0.96(95%CI=0.73,1.27). We did not observe clear associations between blood metal levels and continuous blood pressure measurements.

Conclusion—We did not find overall cross-sectional associations between blood cadmium, lead, mercury, selenium levels and hypertension or blood pressure. We found some evidence suggesting that manganese might be positively associated with risk of hypertension. Associations varied somewhat by race and BMI.

Keywords

Metals; Hypertension; Blood metals; Metal mixture; Biomarkers

1. Introduction

Metals are naturally occurring elements found in the atmosphere, earth's crust, and bodies of water. Metals from anthropogenic activities have increasingly become a source of pollution (Vareda et al., 2019). Exposure to metals occurs through inhalation, dermal contact and ingestion (Tchounwou et al., 2012), and metals from natural as well as anthropogenic sources can bioaccumulate in the human body. Metals such as manganese (Mn) and selenium (Se) are essential elements for physiological and biochemical processes, while nonessential metals such as cadmium (Cd), lead (Pb), and mercury (Hg) are considered toxic to human health; however both classes of metals may cause adverse health effects above certain levels (Azeh Engwa et al., 2019).

Blood concentrations are considered a good biomarker of metal exposure (T. Santonen, 2015). Metal concentrations in blood, however, usually reflect a relatively short-term exposure, with a biological half-life ranging between 75–128 days for Cd, 40–70 days for Hg, 30 days for Pb, 2 hours for Mn, and 100 days for Se (Agency for Toxic Substances and Disease Registry, 1999; Agency for Toxic Substances and Disease Registry, 2012; Ben-Parath et al., 1968; Järup et al., 1983; WHO., 1995). After reaching the blood, metals can bioaccumulate in specific organs, where they may remain for relatively long periods (Rodriguez and Mandalunis, 2018). Cd and Hg are stored mainly in the kidney, and then excreted through feces and urine (Nordberg G.F, 1982; Park and Zheng, 2012). Pb accumulates mainly in mineralizing tissues, such as bones and teeth, and is mostly excreted in urine (Agency for Toxic Substances and Disease Registry, 2017). Mn is most likely to accumulate in liver, brain, and bone (O'Neal and Zheng, 2015) whereas for Se, liver is the

major organ of accumulation (Burk and Hill, 2015). Metal toxicity is thought to be related to the generation of reactive oxidative species which could result in oxidative stress and DNA damage (Tchounwou et al., 2012), and lead to various diseases, including hypertension (Guzik and Touyz, 2017).

Several epidemiological studies have investigated the association between blood metal concentrations and hypertension with inconsistent results. Some studies have found associations of blood Cd with increased blood pressure (Gallagher and Meliker, 2010; Garner and Levallois, 2017). A positive association between blood Hg levels and hypertension was found among individuals with high exposure (Eom et al., 2014; Hu et al., 2017; Hu et al., 2018), but not among those with low to moderate exposure (Hu et al., 2018; Park et al., 2013). The association between blood Mn levels and hypertension is also inconclusive, with positive (Lee and Kim, 2011) and negative associations (Bulka et al., 2019) reported. Occupational epidemiological studies also show that Mn exposure is associated with diastolic hypotension (Jiang and Zheng, 2005). Se is an essential element for antioxidant enzymes, which is believed to have a protective role in the development of hypertension (Duntas, 2009; Kuruppu et al., 2014), but studies have shown that overexposure to Se is associated with increased blood pressure (Vinceti et al., 2019).

In this study, we explored the association between blood metal (Cd, Pb, Hg, Mn, and Se) levels and hypertension among a subset of participants from the GuLF (Gulf Long-term Follow-up) Study. The GuLF Study is a prospective cohort study to investigate potential health effects following the 2010 *Deepwater Horizon* oil spill (Kwok et al., 2019). From 2012 to 2013, a subset of the cohort participants participated in a chemical biomonitoring study and provided blood samples that were used to measure levels of metals (which were not considered to be related to oil spill exposures) as well as chemicals related to exposure to petroleum products (Engel et al., 2017). The prevalence of hypertension varies by race in the U.S., with higher prevalence or greater severity in Black Americans (Bennett et al., 2016). Furthermore, Blacks tend to have higher exposure to toxic chemicals than Whites due to historical patterns of housing segregation (Zwickl et al., 2014). We therefore carried out analyses stratified by race to explore potential effect modification. Obesity (Dludla et al., 2018) and metals (Tchounwou et al., 2012) are both related to oxidative stress, and oxidative stress is a possible mechanism for hypertension (Guzik and Touyz, 2017). Obesity also is a risk factor for hypertension (Whelton et al., 2018). Thus, we additionally conducted analyses stratified by obesity. Finally, we considered associations between the metal mixture and hypertension.

2. Methods

2.1. Study population

The GuLF Study is a large prospective cohort study of individuals (≥21 years of age) who had either participated in oil spill response and clean-up activities for at least 1 day or had completed safety training but were not hired following the 2010 *Deepwater Horizon* oil spill (Kwok et al., 2017). At enrollment (March 2011 to May 2013), participants completed a computer-assisted telephone interview and provided demographic, socioeconomic, lifestyle, and health information. Participants were asked to self-report, separately, race (White,

Black, Asian, and other or multi-racial) and Hispanic ethnicity (Yes, No). For this analysis, we considered race, regardless of Hispanic ethnicity, grouping participants as White, Black, and other (Asian and other/multi-racial). The "other" category was heterogeneous and too small (n=68) for stand-alone analysis. Therefore, they were not considered in race-stratified analyses which focused on Whites and Blacks. English- and Spanish-speaking participants who lived in Alabama, Florida, Louisiana, Mississippi, or eastern Texas were additionally invited to participate in a home visit during which height, weight, and resting blood pressure were measured following a standardized protocol. From September 2012 to May 2013, participants who had not yet completed a home visit were invited to also participate in a chemical biomonitoring study, described in more detail elsewhere (Werder et al., 2018). Participants in the chemical biomonitoring study provided blood samples that were used to measure volatile organic compounds and metals (Cd, Pb, Mn, Hg, and Se). Trained certified medical assistants carried out the home visits and the blood draws. A total of 1,061 participants provided blood samples to measure metal levels.

All home visit participants provided written informed consent. The study was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences. In this cross-sectional analysis, we included 957 participants who had data on blood concentration for at least one metal (missing n=3), baseline blood pressure measurements (missing n=4), information on any anti-hypertensive medication use (missing n=33), and the covariates adjusted for in the model (missing n=64).

2.2. Blood sample collection and exposure assessment

Blood samples were collected into a 6mL royal blue top EDTA trace metals tube (Becton Dickinson Vacutainer® tubes) to measure concentrations of metals (Cd, Pb, Mn, total Hg, and Se) and were shipped on cold packs by priority overnight service to the central processing lab (Engel et al., 2017). The blood samples were sent in biweekly batches to the Centers for Disease Control and Prevention, Environmental Health Sciences Laboratory in Atlanta, Georgia for analysis using mass spectrometry following a standard protocol (National Center for Environmental Health, 2012). Internal standards were at a constant concentration in all QC samples. Data from blind QC samples were used to estimate variation for internal (within laboratory) consistency. We collected duplicate blood samples from randomly selected individuals, and evaluated variability across paired samples.

The assay limits of detection (LODs) were 0.16ng/mL for Cd, 0.25ng/mL for Pb, 0.16ng/mL for Hg, 1.06ng/mL for Mn, and 30ng/mL for Se. For samples with biomarker levels below the LOD, the levels were substituted with a standard measurement calculated as LOD/√2. The numbers of samples below the LOD were 138 (14%) for Cd, 2 (0.2%) for Pb, and 16 (1.7%) for Hg. All Mn and Se samples were above the LOD. Se is a non-metallic chemical element, but for brevity we refer to all the elements considered in this study as metals.

2.3. Outcome assessment

Blood pressure was measured during the home visit following a standardized protocol where 3 measurements were taken in a seated position after a 5-minute rest (Kwok et al., 2017). The average of the last 2 measurements was used as the subjects' blood pressure. The

definition of hypertension was as follows: 1) either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; or 2) currently taking antihypertensive medication (n=193). When using continuous blood pressure as the outcome variable, we corrected the blood pressure of those who reported taking any antihypertensive medication by adding 15 mm Hg to their measured systolic blood pressure and 10 mm Hg to their measured diastolic blood pressure (Baguet et al., 2007; Tobin et al., 2005).

2.4. Statistical analysis

Blood metal concentrations were divided into quartiles based on the distributions in the study samples. Restricted quadratic splines analyses indicated that quartiles and tertiles fit the model well, and we chose quartiles to better explore potential dose-response relationships (Howe et al., 2011). Spearman rank correlation was used to estimate correlation coefficients among blood metal concentrations. We used multivariable Poisson regression with robust error variance to estimate prevalence ratios (PR) and 95% confidence intervals (CIs) for hypertension associated with each metal (first quartile as referent). We fit the median of each quartile group as a continuous variable in models for trend tests. We additionally used multivariable general linear models to investigate the associations between metals and continuous blood pressure. We also explored the associations between continuous blood metal levels and hypertension as well as blood pressure.

A directed acyclic graph (DAG) was used to select covariates for adjustment in the models (Figure S1). Models were adjusted for age (≤30, 31–40,41–50, 51–60, and >60 years), sex (male and female), race (White and non-White), educational attainment (less than high school, high school diploma, some college, and college graduate or higher), and income level (≤$20,000, $20,001-$50,000, and >$50,000). Body mass index (BMI) was defined as a person's weight (kilogram) divided by the square of the person's height (meter), and obesity was defined as BMI≥30 (World Health Organization). We also conducted stratified analyses according to race, BMI, and sex. We added interaction terms into the models to explore potential modification of associations between metals and hypertension by stratification factors.

To explore the relationship between the metal mixture and hypertension, we used quantile-based g-computation to estimate the mixture odds ratio (OR) and relative contribution (weight) of each metal (Keil et al., 2020). Quartile-based g-computation estimates the joint effect of the mixture when simultaneously increasing all metals by a single quantile. This method does not require the same effect direction of exposures in the mixture and can yield an unbiased estimate when the sample size is small or moderate or when there is unmeasured confounding. Since studies have shown that Se may be a protective factor for hypertension (Flores-Mateo et al., 2006; Kuruppu et al., 2014), we repeated the mixture analysis excluding Se.

Statistical significance was defined as $p<0.05$ (two-tailed). We also conducted the following sensitivity analyses: (1) including all five metals simultaneously in one model to evaluate the effect of co-exposure to these metals; (2) limiting the individual metal and metal mixture analyses to non-smokers; (3)additionally adjusting for smoking status and alcohol consumption; (4) using the updated definition of hypertension (systolic blood pressure

>130 or diastolic blood pressure >80) released by the American College of Cardiology and the American Heart Association (Whelton et al., 2018) as the outcome; and (5) additionally adjusting for ordinal estimates of maximum daily total hydrocarbon (THC) exposure experienced during oil spill cleanup (Stewart et al., 2018). Analysis was done using SAS 9.4 software (SAS Institution, Inc., Cary, NC). Quantile-based g-computation was done using R 3.6.1 package “qgcomp” (Keil et al., 2020).

3. Results

Table 1 shows characteristics of the hypertensive (34%) and non-hypertensive (66%) participants. Hypertensive participants were more likely to be older, male, White, obese, and have lower educational attainment but higher household income.

The median of blood metal levels among participants was 0.4ng/mL for Cd, 1.2ng/mL for Pb, 0.9ng/mL for Hg, 8.4ng/mL for Mn, and 198.0ng/mL for Se (table S1). The correlations among blood metal concentrations were low to moderate (table S2).

We did not find significant associations between blood metal levels and prevalence of hypertension. Comparing the highest quartile of exposure with the lowest (Q4vs1), the estimated PR was less than or equal to 1.0 for Cd (PR=0.92, 95%CI=0.73,1.15), Pb (PR=0.86, 95%CI=0.66,1.12), Hg (PR=0.89, 95%CI=0.71,1.12), and Se (PR=1.00, 95%CI=0.80,1.26). The association between Mn and hypertension was suggestively positive with a PR of 1.22 (95%CI=0.95,1.57) (table 2). Similarly, we found no significant associations between continuous blood metal concentrations and risk of hypertension (table S3).

The joint effect of increasing all five metals by one quartile on risk of hypertension was 0.96 (95%CI=0.73,1.27) (table S4). The summary ORs were 1.15 for metals with a positive association with hypertension and 0.84 for those with an inverse association. Mn and Se were positively weighted in the mixture, with Mn (0.62) having the greatest proportional positive contribution to the joint effect. Pb, Hg, and Cd were negatively weighted with risk of hypertension, and Pb (0.45) had the greatest proportional negative contribution to the joint effect. When we repeated the mixture analysis excluding Se, the joint effect of increasing the remaining four metals (Cd, Pb, Hg, and Mn) by one quartile on risk of hypertension was 0.92 (95%CI: 0.72,1.19).

In analyses stratified by race, there were too few participants classified as other race (n=68) to support a stand-alone analysis. Thus, only results for those classified as White or Black are shown. Although we did not observe significant interaction between race and any blood metal levels (table S5), we observed some qualitative differences in direction and magnitude of associations (table 3). The PR(Q4vs1) for Hg was 0.69 (95%CI=0.53, 0.91) in White participants and 1.29 (95%CI=0.86,1.92) in Black participants (p for interaction=0.5, table S5, table 3). For Mn, we observed higher estimated PRs and a suggestive dose-response relationship among Black participants. The corresponding PRs (Q4vs1) were 1.15 (95%CI=0.83, 1.60) in White participants and 1.37 (95% CI=0.92, 2.05) in Black participants (p for interaction=0.5, table S5, table 3). In analyses of continuous

blood pressure (table S6), we found that there was a significant interaction between Mn and race (p for interaction=0.02, table S6). The PR was 1.05 (95%CI=1.01,1.09) among Black participants and 1.00 (95%CI=0.98,1.03) among White participants for one unit increase in blood Mn concentration.

In analyses stratified by BMI, we did not find significant interactions between obesity and blood metal levels, but the directions of stratum-specific association differed by obesity. For example, elevated PRs(Q4vs1) were seen for Cd (PR= 1.19, 95%CI=0.91,1.56; p for interaction=0.5), Pb (PR =1.14, 95%CI=0.84,1.55; p for interaction=1.0), and Mn (PR=1.25, 95%CI=0.93,1.68; p for interaction=0.8) among obese (BMI≥30) participants, but not among those who were not obese (BMI<30) (table 4, table S5). We observed few differences in analyses stratified by sex (table S7), although the PR for Mn among males (PR[Q4vs1]=1.20, 95% CI=0.91, 1.59) was higher compared with females (PR[Q4vs1]=1.01, 95% CI=0.58, 1.74; p for interaction=0.2).

Analyses using continuous blood pressure measurements identified no clear associations with blood metal levels (table 5). Results were similar in sensitivity analyses: (1) with mutual adjustment for all five metals (table S8), (2) additionally adjusting for smoking status and alcohol consumption (table S8), (3) using the updated definition of hypertension (table S8), (4) limiting individual and mixture analyses to non-smokers (table S9, table S10), and (4) additionally adjusting for spill cleanup-related daily maximum THC ordinal exposure level (table S11). Lastly, we observed no differences when we compared blood metal concentrations between oil spill workers and non-workers (table S12).

4. Discussion

In our study, we did not find overall associations between blood metal levels and prevalent hypertension that met traditional thresholds of statistical significance (i.e., $p<0.05$), either for individual metal or for the metal mixture. In stratified analyses, however, there were some suggestions of differences by race and BMI categories.

4.1. Cadmium (Cd)

The association between Cd exposure and hypertension in previous research has been inconsistent. Results from the 2005 Korean National Health and Nutrition Examination Survey (NHANES) indicate that blood Cd is associated with increased odds of hypertension and blood pressure, but the participants in that study had a relatively higher level of mean blood Cd (1.64μg/L for non-hypertensive and 1.77μg/L for hypertensive participants) compared to participants in our study (0.4ng/mL for both hypertensive and non-hypertensive participants) (Eum et al., 2008). Another study based on the U.S. NHANES reported no association between blood Cd and prevalence of hypertension; these NHANES participants had a mean Cd level of 3.77nmol/L (0.42ng/mL), which was lower than that of the Korean NHANES participants and similar to the levels observed in our sample (Tellez-Plaza et al., 2008). Some other studies found that urinary Cd is associated with lower risk of hypertension (Gallagher and Meliker, 2010). However, urinary Cd represents long-term exposure, and the nephrotoxicity of Cd may result in lower urinary Cd concentration in the long run (Jarup and Akesson, 2009).

Cd is absorbed through inhalation and ingestion, and smokers tend to have higher Cd exposure (Garner and Levallois, 2016). When smoking, cadmium is converted to cadmium oxide, which is then inhaled, and 20–50% of Cd is deposited in blood (Bernhard et al., 2005). In sensitivity analyses stratified by smoking status and additionally adjusting for smoking status, we did not see any significant associations.

4.2. Lead (Pb)

Many epidemiological studies have provided evidence that blood Pb is associated with increased blood pressure and risk of hypertension, but the dose-response relationship and associations with low level exposure are uncertain (Navas-Acien et al., 2007). One study suggested a threshold effect for the association between blood pressure and blood Pb below 50μg/L (Gambelunghe et al., 2016). In our study, the median blood Pb level is 1.2ng/mL which is lower than the proposed threshold of 50μg/L and is also lower than blood Pb levels reported in other studies that observed positive associations (Gambelunghe et al., 2016; Harlan, 1988). Mean blood Pb concentration in the U.S. NHANES from 2011–2016 was 0.973μg/dL, which is also higher than that of participants in our study (Centers for Disease Control and Prevention, 2021). We did not observe a significant association between blood Pb and either blood pressure or prevalence of hypertension, although PRs were suggestively elevated among those who were obese.

4.3. Mercury (Hg)

In our study, levels of blood Hg ranged from 0.1–25.0 ng/ml, with a median of 0.9 ng/ml. We saw no evidence of hypertension risk with increasing blood levels of total Hg in our study. Hair Hg concentrations and blood Hg concentrations have good correlations and a hair-to-blood ratio of 250 is recommended for conversion (Organization, 1990). In a meta-analysis, Hu et al. reported no association for low-to-moderate Hg exposure (hair mercury < 2μg/g or blood mercury < 8μg/L), but a positive association for high Hg exposure (hair mercury ≥ 2μg/g or blood mercury ≥ 8μg/L), and suggested an exposure threshold in hair Hg levels of 2–3 μg/g or equivalent for an association between Hg exposure and hypertension (Hu et al., 2018). Several other studies reported inverse associations with hypertension among populations with blood Hg levels below 8μg/L (Park et al., 2013; Vupputuri et al., 2005). The different results may be because hair and blood Hg usually represents long-term and short-term exposure, respectively (Agency for Toxic Substances and Disease Registry, 1999).

In our study, the results suggest an inverse association between blood Hg and prevalence of hypertension. The ratio of methylmercury to total Hg in blood is 67–85% (Mortensen et al., 2014), and methylmercury exposure comes primarily from fish consumption (United States Environmental Protection Agency, 1997). Fish also contains nutrients such as omega-3 fatty acids, which are a protective factor for hypertension (Morris et al., 1993). Studies have shown that the association between blood Hg and blood pressure differs between fish-consumers and non-fish consumers, with a positive association between total blood Hg and blood pressure in non-fish consumers (Vupputuri et al., 2005). Thus, the potential inverse association might be due to fish consumption in the coastal GuLF Study population. Consuming more fish may lead to greater intake of some nutrients, such as omega-3 fatty

acids, which in turn results in a higher blood Hg level, which on balance results in lower risk of hypertension. The sample size in our study was too small to consider seafood consumption in detail, but in a model where we adjusted for any seafood consumption in the last 24 hours results for Hg were unchanged.

4.4. Manganese (Mn)

Mn is an essential metal and is a cofactor for antioxidant enzymes, which helps reduce reactive oxygen species and prevent oxidative stress (Rines and Ardehali, 2013). As oxidative stress is a possible mechanism for hypertension, adequate Mn intake may decrease the risk of hypertension. Nevertheless, excess exposure to Mn may increase oxidative stress (Li and Yang, 2018).

The results for epidemiological studies of the association between Mn and hypertension have been inconsistent. A study investigating people in the Normative Aging Study found a negative association between toenail Mn and blood pressure (Mordukhovich et al., 2012). The results from a Korean NHANES showed an increased risk of hypertension associated with blood Mn levels (Lee and Kim, 2011). The inconsistent results might be due to different half-lives in different biomarkers. Toenail Mn reflects cumulative exposure over as much as 7–12 months (Laohaudomchok et al., 2011), but blood Mn has a short biological half-life (Agency for Toxic Substances and Disease Registry, 2012). In an epidemiological study considering occupational exposure to Mn, Mn exposure was associated with higher risk of diastolic hypotension (Jiang and Zheng, 2005).

In our study, the median Mn levels was 8.4ng/mL, which is lower than studies conducted in Korean, and is also lower than samples from the 2011–2016 U.S. NHANES (9.35μg/L) (Centers for Disease Control and Prevention, 2021). We found a positive association between blood Mn and prevalent hypertension, with a non-significant association among all participants and a significant association among never-smokers.

4.5. Selenium (Se)

Se is a critical component of antioxidant enzymes, and may be a protective factor for hypertension (Rayman, 2000). Several clinical trials have shown that Se supplementation is associated with lower blood pressure, but these studies also investigated other simultaneous interventions, such as vitamin and fiber supplementation (Kuruppu et al., 2014; Shargorodsky et al., 2010; Singh et al., 1992).

The association between environmental Se exposure and hypertension is still unclear (Kuruppu et al., 2014). Several prospective studies reported an association between blood Se levels and lower blood pressure (Bulka et al., 2019; Nawrot et al., 2007), but another prospective study did not find an association between plasma Se and blood pressure (Arnaud et al., 2007). A study of individuals living in a seleniferous area with overexposure (median serum Se: 171.3μg/L) to environmental Se reported an association with increased blood pressure (Vinceti et al., 2019). Blood Se concentrations in participants in our study (198 ng/mL) were relatively higher than those in the above two studies that found inverse associations [122μg/L (Bulka et al., 2019) and 113μg/L (Nawrot et al., 2007)], and the same as participants from U.S. NHANES (mean blood Se concentration: 190μg/L) (Centers

for Disease Control and Prevention, 2021). The relationship between Se and blood pressure also varies by sex, with a stronger association observed among females (Laclaustra et al., 2009; Vinceti et al., 2019). In our study, we did not find an association between Se exposure and hypertension, among all subjects nor in either sex.

4.6. Stratification by race and BMI

The prevalence of hypertension is notably higher among Blacks than among Whites in the U.S. (Bennett et al., 2016). Environmental exposures also vary by race, with Blacks more likely to be living in areas with higher levels of pollution compared with Whites (Zwickl et al., 2014). Considering the differences in prevalence of hypertension and exposure opportunities, we carried out analyses stratified by race. In these analyses, Hg was positively associated with hypertension in Black participants but inversely associated among White participants. Blood Hg levels also differed, with relatively higher levels among White participants (median: 1.1ng/mL), however, than among Black participants (median: 0.8ng/mL). Blood Hg levels may be related to fish consumption rather than environmental exposures and there may be beneficial effects from consumption of specific fatty acids in fish (Morris et al., 1993). In the U.S. NHANES, Whites were found to consume more marine fish than Blacks (Environmental Protection Agency, 2014). For Mn, the risk of hypertension was relatively higher among Black participants than Whites, and we found an interaction between continuous blood Mn concentration and race. These observations are consistent with the results of a study reporting that the effect of airborne metals was stronger among participants of other races/ethnicities than Whites participants (Xu et al., 2020).

Obesity is a risk factor for hypertension (Whelton et al., 2018), and an epidemiological study showed that blood metal levels are related to obesity (Wang et al., 2018). Obesity may be a modifier or a mediator of the association between blood metal levels and hypertension. Thus, we conducted analyses stratified by BMI and observed positive associations of blood Cd, Pb, and Mn levels with risk of hypertension only among obese participants. Obese participants may be more susceptible to effects of an environmental exposure such as metals. An epidemiological study shows that when exposed to higher levels of metal particulates, the cardiovascular effect was aggravated among obese people (Chen et al., 2007). The possible mechanism may be an stronger inflammatory responses among obese people (Shore et al., 2003).

4.7. Strengths and limitations

This study has notable strengths. We measured blood pressure, height, and weight following a standard protocol instead of using self-reported information, so hypertension status and obesity could be assessed more accurately. In addition, a national reference laboratory was used to measure the blood metal concentrations.

There are also several limitations in this study. First, this is a cross-sectional study. Blood samples and blood pressure measurements were collected at the same time, so we cannot evaluate temporal relationships between metal exposure and hypertension. Participants in the GuLF Study cohort might be impacted by other pollutants, such as volatile organic compounds, and many of the participants worked on cleanup or response following the

Deepwater Horizon oil spill, limiting generalizability. However, we conducted a sensitivity analysis additionally adjusting for oil spill cleanup-related THC exposure, and the results did not change. Considering the relatively wide CIs and small magnitudes of β coefficients when using continuous blood pressure as the outcome variable, the sample size of our study might be underpowered to detect significant effects of this magnitude.

5. Conclusions

We did not find evidence indicating cross-sectional associations between blood levels of Cd, Pb, Hg, or Se and either prevalent hypertension or blood pressure overall. Since the participants in this study had relatively low levels of Cd, Pb, and Hg, the results of this study raise the possibility of no associations between these metals and hypertension under a certain threshold. We also found some evidence suggesting that Mn might be associated with higher risk of hypertension even at low levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Human subject study

The institutional review board (IRB) of the National Institute of Environmental Health Sciences approved the GuLF Study.

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Table 1.

Characteristics of hypertensive and non-hypertensive participants [n (%)]

	Full population (n=957)	Hypertensive (n=328)	Non-hypertensive (n=629)
Age (years)			
≤30	218 (23)	23 (7)	195 (31)
31–40	237 (25)	57 (17)	180 (29)
41–50	243 (25)	87 (27)	156 (25)
51–60	190 (20)	108 (33)	82 (13)
>60	69 (7)	53 (16)	16 (3)
Sex			
Male	711 (74)	256 (78)	455 (72)
Female	246 (26)	72 (22)	174 (28)
Race			
White	476 (50)	189 (58)	287 (46)
Non-White	481 (50)	139 (42)	342 (54)
Black	413 (43)	120 (37)	293 (47)
Other [a]	68 (7)	19 (6)	49 (8)
Annual household Income ($)			
≤20,000	418 (44)	122 (37)	296 (47)
20,001–50,000	333 (35)	126 (38)	207 (33)
>50,000	206 (22)	80 (24)	126 (20)
Highest educational attainment			
Less than high school	200 (21)	81 (25)	119 (19)
High school diploma	355 (37)	120 (37)	235 (37)
Some college	289 (30)	89 (27)	200 (32)
College graduate or higher	113 (12)	38 (12)	75 (12)
Smoking status			
Current smoker	289 (30)	100 (30)	189 (30)
Former smoker	187 (20)	79 (24)	108 (17)
Never smoked	481 (50)	149 (45)	332 (53)
Alcohol consumption			
Current drinker	657 (69)	226 (69)	431 (69)
Former drinker	208 (22)	81 (25)	127 (20)
Never drank	92 (10)	21 (6)	71 (11)
BMI (kg/m^2)			
<30	515 (54)	129 (39)	386 (61)
≥30	442 (46)	199 (61)	243 (39)

[a] Other includes Asian, other/multi-racial

Percentage may not equal 100% due to rounding.

Table 2.

Blood metal concentrations and overall risk of hypertension (n=957)

	Full population (n)	Hypertensive [n (%)]	Blood metal concentrations [M (Min, Max), ng/mL]	PR (95%CI)
Cadmium (Cd) [a]				
Quartile 1	310	106 (34)	0.2 (0.07,0.2)	1 (referent)
Quartile 2	130	49 (38)	0.3 (0.3,0.3)	0.90 (0.70,1.14)
Quartile 3	277	94 (34)	0.5 (0.4,0.8)	0.92 (0.74,1.13)
Quartile 4	234	79 (34)	1.4 (0.9,5.0)	0.92 (0.73,1.15)
p for trend				0.7
Lead (Pb)				
Quartile 1	261	66 (25)	0.6 (0.2,0.8)	1 (referent)
Quartile 2	228	73 (32)	1.1 (0.9,1.2)	0.96 (0.73,1.25)
Quartile 3	236	92 (39)	1.5 (1.3,1.9)	0.91 (0.71,1.17)
Quartile 4	232	97 (42)	2.7 (2.0,33.8)	0.86 (0.66,1.12)
p for trend				0.4
Mercury (Hg)				
Quartile 1	242	76 (31)	0.4 (0.1,0.5)	1 (referent)
Quartile 2	238	73 (31)	0.7 (0.6,0.9)	0.88 (0.69,1.12)
Quartile 3	230	81 (35)	1.3 (1.0,1.8)	0.88 (0.70,1.12)
Quartile 4	247	98 (40)	3.1 (1.9,25.0)	0.89 (0.71,1.12)
p for trend				0.7
Manganese (Mn)				
Quartile 1	239	68 (28)	6.0 (2.5,6.8)	1 (referent)
Quartile 2	247	87 (35)	7.7 (6.9,8.4)	1.17 (0.92,1.49)
Quartile 3	228	84 (37)	9.4 (8.5,10.5)	1.14 (0.89,1.46)
Quartile 4	243	89 (37)	12.4 (20.6,33.1)	1.22 (0.95,1.57)
p for trend				0.3
Selenium (Se)				
Quartile 1	238	87 (37)	173.4 (124.9,184.1)	1 (referent)
Quartile 2	239	74 (31)	191.8 (184.2,197.9)	0.91 (0.72,1.14)
Quartile 3	241	85 (35)	206.2 (198.0,215.6)	1.03 (0.82,1.28)
Quartile 4	239	82 (34)	229.1 (215.7,366.8)	1.00 (0.80,1.26)
p for trend				0.8

Models were adjusted for age, sex, race, educational attainment, and household income level.

[a]Missing n=6.

Table 3.

Blood metal concentrations and risk of hypertension stratified by self-reported race

		White			Black		
		Full population (n)	**Hypertensive [n (%)]**	**PR (95%CI)**	**Full population (n)**	**Hypertensive [n (%)]**	**PR (95%CI)**
Cadmium (Cd) [a]	Quartile 1	176	63 (36)	1 (referent)	112	35 (31)	1 (referent)
	Quartile 2	63	32 (51)	1.10 (0.83,1.46)	57	16 (28)	0.70 (0.44,1.10)
	Quartile 3	127	52 (41)	1.07 (0.82,1.39)	128	34 (27)	0.70 (0.48,1.04)
	Quartile 4	106	42 (40)	1.03 (0.77,1.37)	115	35 (30)	0.83 (0.58,1.19)
	p for trend			1.0			0.9
Lead (Pb)	Quartile 1	110	33 (37)	1 (referent)	127	30 (24)	1 (referent)
	Quartile 2	105	39 (37)	1.05 (0.74,1.49)	107	28 (26)	0.85 (0.54,1.34)
	Quartile 3	138	60 (43)	0.97 (0.71,1.32)	85	26 (31)	0.84 (0.53,1.33)
	Quartile 4	123	57 (46)	0.88 (0.63,1.21)	94	36 (38)	0.90 (0.55,1.45)
	p for trend			0.4			0.9
Mercury (Hg)	Quartile 1	101	44 (43)	1 (referent)	125	29 (23)	1 (referent)
	Quartile 2	102	39 (38)	0.79 (0.58,1.06)	120	29 (24)	0.98 (0.64,1.48)
	Quartile 3	118	47 (40)	0.72 (0.54,0.96)	95	30 (32)	1.15 (0.75,1.77)
	Quartile 4	155	59 (38)	0.69 (0.53,0.91)	73	32 (44)	1.29 (0.86,1.92)
	p for trend			0.2			0.3
Manganese (Mn)	Quartile 1	78	28 (35)	1 (referent)	151	37 (25)	1 (referent)
	Quartile 2	121	54 (45)	1.25 (0.91,1.72)	108	29 (27)	1.04 (0.70,1.54)
	Quartile 3	140	52 (37)	1.01 (0.73,1.41)	75	25 (33)	1.31 (0.88,1.96)
	Quartile 4	137	55 (40)	1.15 (0.83,1.60)	79	29 (37)	1.37 (0.92,2.05)
	p for trend			0.8			0.2
Selenium (Se)	Quartile 1	114	47 (41)	1 (referent)	108	36 (33)	1 (referent)
	Quartile 2	101	40 (40)	1.00 (0.75,1.34)	122	29 (24)	0.77 (0.52,1.13)
	Quartile 3	128	50 (39)	1.05 (0.80,1.38)	95	28 (29)	1.00 (0.67,1.48)
	Quartile 4	133	52 (39)	1.09 (0.82,1.43)	88	27 (31)	1.00 (0.68,1.47)
	p for trend			0.7			0.8

Models were adjusted for age, sex, educational attainment, and household income level.

[a] Missing n=6.

Table 4.

Blood metal concentrations and risk of hypertension stratified by BMI

		BMI≥30			BMI<30		
		Full population (n)	**Hypertensive [n (%)]**	**PR (95%CI)**	**Full population (n)**	**Hypertensive [n (%)]**	**PR (95%CI)**
Cadmium (Cd) [a]	Quartile 1	170	71 (42)	1 (referent)	140	35 (25)	1 (referent)
	Quartile 2	71	40 (56)	1.05 (0.82,1.35)	59	9 (15)	0.61 (0.33,1.12)
	Quartile 3	124	50 (40)	1.00 (0.77,1.29)	153	44 (29)	0.95 (0.66,1.35)
	Quartile 4	77	38 (49)	1.19 (0.91,1.56)	157	41 (26)	0.89 (0.61,1.30)
	p for trend			0.4			0.9
Lead (Pb)	Quartile 1	147	47 (32)	1 (referent)	114	19 (17)	1 (referent)
	Quartile 2	112	51 (46)	1.05 (0.78,1.42)	116	22 (19)	0.89 (0.52,1.52)
	Quartile 3	108	57 (53)	1.09 (0.82,1.45)	128	35 (27)	0.81 (0.50,1.31)
	Quartile 4	75	44 (59)	1.14 (0.84,1.55)	157	53 (34)	0.82 (0.50,1.32)
	p for trend			0.6			0.6
Mercury (Hg)	Quartile 1	113	48 (42)	1 (referent)	129	28 (22)	1 (referent)
	Quartile 2	123	50 (41)	0.92 (0.70,1.21)	115	23 (20)	0.75 (0.47,1.19)
	Quartile 3	99	43 (43)	0.93 (0.69,1.24)	131	38 (29)	0.94 (0.63,1.39)
	Quartile 4	107	58 (54)	0.96 (0.74,1.25)	140	40 (29)	0.82 (0.55,1.22)
	p for trend			1.0			0.6
Manganese (Mn)	Quartile 1	93	38 (41)	1 (referent)	146	30 (21)	1 (referent)
	Quartile 2	118	51 (43)	1.07 (0.79,1.45)	129	36 (28)	1.14 (0.78,1.67)
	Quartile 3	107	51 (48)	1.03 (0.76,1.38)	121	33 (27)	1.11 (0.74,1.69)
	Quartile 4	124	59 (48)	1.25 (0.93,1.68)	119	30 (25)	0.99 (0.65,1.51)
	p for trend			0.3			0.9
Selenium (Se)	Quartile 1	107	55 (51)	1 (referent)	131	32 (24)	1 (referent)
	Quartile 2	111	45 (41)	0.88 (0.68,1.15)	128	29 (23)	0.96 (0.66,1.42)
	Quartile 3	126	54 (43)	0.88 (0.68,1.13)	115	31 (27)	1.19 (0.81,1.75)
	Quartile 4	98	45 (46)	0.97 (0.75,1.25)	141	37 (26)	1.12 (0.77,1.64)
	p for trend			0.9			0.5

Models were adjusted for age, sex, race, educational attainment, and household income level.

[a] Missing n=6.

Table 5.

Blood metal concentrations and blood pressure

		N	DBP (β [95%CI])	SBP (β[95%CI])
Cadmium (Cd) [a]	Quartile 1	310	0 (referent)	0 (referent)
	Quartile 2	130	−0.13 (−2.42,2.16)	0.73 (−2.56,4.02)
	Quartile 3	277	−0.33 (−2.15,1.48)	−1.79 (−4.40,0.81)
	Quartile 4	234	−0.88 (−2.81,1.05)	−2.04 (−4.81,0.74)
	p for trend		0.4	0.1
Lead (Pb)	Quartile 1	261	0 (referent)	0 (referent)
	Quartile 2	228	0.21 (−1.81,2.24)	1.19 (−1.73,4.11)
	Quartile 3	236	0.26 (−1.84,2.35)	0.54 (−2.48,3.55)
	Quartile 4	232	−0.01 (−2.21,2.19)	−0.96 (−4.13,2.22)
	p for trend		0.9	0.3
Mercury (Hg)	Quartile 1	242	0 (referent)	0 (referent)
	Quartile 2	238	0.43 (−1.54,2.39)	0.13 (−2.71,2.97)
	Quartile 3	230	0.73 (−1.29,2.76)	−0.15 (−3.07,2.77)
	Quartile 4	247	0.23 (−1.80,2.26)	−0.79 (−3.72,2.14)
	p for trend		1.0	0.5
Manganese (Mn)	Quartile 1	239	0 (referent)	0 (referent)
	Quartile 2	247	0.61 (−1.37,2.60)	2.18 (−0.68,5.03)
	Quartile 3	228	0.17 (−1.89,2.23)	−1.01 (−3.97,1.95)
	Quartile 4	243	0.60 (−1.44,2.64)	1.86 (−1.08,4.79)
	p for trend		0.7	0.5
Selenium (Se)	Quartile 1	238	0 (referent)	0 (referent)
	Quartile 2	239	0.70 (−1.28,2.68)	0.04 (−2.82,2.90)
	Quartile 3	241	0.97 (−1.02,2.95)	1.02 (−1.84,3.89)
	Quartile 4	239	1.66 (−0.34,3.67)	0.93 (−1.97,3.83)
	p for trend		0.1	0.4

Models were adjusted for age, sex, race, educational attainment, and household income level.

DBP: diastolic blood pressure; SBP: systolic blood pressure.

[a]Missing n=6.