The contribution of declines in lead exposure to reductions in blood pressure levels: Longitudinal evidence in the Strong Heart Family Study

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ABSTRACT

Background: Chronic lead exposure in adults is associated with subclinical and clinical cardiovascular disease. However, the reversibility of these cardiovascular effects if lead exposure is removed is largely unknown. American Indian (AI) participants in the Strong Heart Family Study (SHFS) experienced a 23% decline in blood lead concentrations in recent decades. We evaluated if declines in blood lead were associated with changes in systolic and diastolic blood pressure in the SHFS.

Methods: Lead was measured in whole blood samples from 285 SHFS participants at both Phase 3 (1997-1999) and Phase 5 (2006-2009) study visits. Measures of cardiac geometry and functioning, including blood pressure, were assessed in 2001-2003 and 2006-2009. We evaluated the association between declines in blood lead and changes in blood pressure via generalized estimating equations a) across tertiles of lead decline, b) per decline in lead corresponding to the interquartile range (IQR), and c) in flexible cubic spline models. Secondary analyses considered associations with other measures of cardiac functioning and geometry measured via transthoracic echocardiograms.

Results: Mean blood lead was 2.04 µg/dL at baseline. Mean decline in blood lead was 0.67 µg/dL overall, 1.78 µg/dL for participants in the highest tertile of decline, and -0.33 µg/dL (an increase) for participants in the lowest tertile of decline. In fully adjusted models, the mean difference in the change in systolic blood pressure comparing the highest tertile of decline in blood lead to the lowest tertile was -7.1 mmHg (95% CI -13.2, -1.0). Flexible cubic spline models indicated a significant but non-linear association between decline in blood lead and declines in systolic blood pressure, with significant, linear associations beyond declines in blood lead of 0.1 µg/dL or higher. Declines in blood lead were inversely but non-significantly

associated with declines in diastolic blood pressure, and were also associated with declines in midwall shortening and interventricular septum in systole.

Conclusions: Despite sample size limitations, declines in blood lead levels were associated with reductions in systolic blood pressure in the SHFS, even at very low declines in blood lead levels (<1 µg/dL). These findings support the importance of further reducing lead exposures for all US communities.

INTRODUCTION

Over the past several decades, US regulatory changes and public health policies successfully reduced lead emissions and lead exposures nationwide, including bans on lead in gasoline, residential paint, plumbing components, and food cans, and the regulation of lead in public drinking water (Brown and Margolis 2012; A. E. Nigra and A. Navas-Acien 2021). As a result, both adult and child blood lead levels in the US have decreased substantially, although lead remains ubiquitous in the environment and major racial/ethnic inequities in lead exposure persist (Egan et al. 2021; Ettinger et al. 2020; Hanna-Attisha et al. 2018; McFarland et al. 2022).

Substantial evidence supports that lead is an independent risk factor for the development of cardiovascular disease and mortality (Lamas et al. 2021; Navas-Acien et al. 2007; Navas-Acien 2021; Ruiz-Hernandez et al. 2017). In NHANES (National Health and Nutrition Examination Survey), declines in blood lead levels observed in the general US population over several decades were associated with subsequent reductions in cardiovascular mortality (Ruiz Hernandez et al. 2017). Consistent evidence from experimental models and epidemiologic studies also support that lead exposure is causally associated with elevated blood pressure and hypertension, likely through oxidative stress, altering vascular reactivity, angiotensin system dysfunction, and vasomodulator imbalance (Gonick 2002; United States Environmental Protection Agency 2013; Vaziri and Khan 2007). Lead exposure has also been specifically associated with measures of left ventricular function and structure, including left ventricular hypertrophy, independently of blood pressure levels (Navas-Acien et al. 2007; Yang et al. 2017). However, most studies on the association between lead exposure and blood pressure and left ventricular function and structure have been conducted at high blood lead levels (>20 µg/dL), and epidemiologic evidence at currently low blood lead levels (<3 µg/dL) is limited (United

States Environmental Protection Agency 2013).

American Indian (AI) communities experience both a high burden of cardiovascular disease and elevated chronic metal exposures compared to the general US population (Lee et al. 1990; Pang et al. 2016). The Strong Heart Study (SHS) and the Strong Heart Family Study (SHFS, the family-based cohort extension) are the largest epidemiologic cohorts of AI adults followed specifically to study cardiovascular disease and its risk factors. Recently, two sub-studies conducted at Columbia University and the Centers for Disease Control and Prevention (CDC) measured blood lead concentrations in a subset of participants from two study visits occurring from 1997-1999 and 2006-2009. Using these data, we recently estimated that mean within-person blood lead declined by 23% over this period (mean 2.5% yearly decline) (Nigra et al. 2021), similar to relative population-level declines estimated in NHANES during this time period. Few studies, however, have evaluated if a decline in lead exposure results in short-term positive changes in blood pressure and left ventricular function and structure. If short-term benefits are observed, these findings could explain at least part of the long-term benefit on cardiovascular mortality observed in NHANES.

Our objective was to evaluate if declines in blood lead concentrations were associated with changes in systolic and diastolic blood pressure and other metrics of cardiac geometry and functioning over time in the SHFS. Our primary outcomes were changes in systolic and diastolic blood pressure, with secondary analyses considering other metrics of cardiac geometry and functioning measured via transthoracic echocardiograms. We hypothesized that declines in blood lead would be associated with declines in both systolic and diastolic blood pressure over time, and with improvements in other measures of cardiac geometry and functioning.

MATERIALS AND METHODS

Study population

The SHS is an ongoing, prospective, population-based cohort of 4,549 AI adults from thirteen tribes and communities in rural Arizona, Oklahoma, and North Dakota and South Dakota, originally developed to evaluate cardiovascular disease and its risk factors. All adults 45–74 years of age at baseline were invited to participate in the Phase 1 baseline exam (1989-1991) (Lee et al. 1990; Welty et al. 1995). The participation rate was 62% overall (Stoddart et al. 2000). Participants were re-evaluated at Phase 2 (1993-1995), Phase 3 (1997-1999), Phase 4 (2001-2003), and Phase 5 (2006-2009) study visits. To extend the SHS into a multigenerational cohort derived from the original SHS families, the SHFS was initiated with a pilot study conducted during SHS Phase 3 (1997-1999). Families were eligible if they had a core sibship consisting of 3 original SHS participants and at least 5 additional living family members (North et al. 2003). Additional SHS cohort family members 15 years of age and older were enrolled during the first SHFS visit at Phase 4 (2001-2003).

In our current analysis, participants were eligible for inclusion if they had whole blood samples available during both Phase 3 (either the SHS Phase 3 exam or the SHFS Phase 3 pilot) and Phase 5 visits. In a sub-study funded by a National Institute for Environmental Health Sciences pilot award at Columbia University, 150 participants with whole blood samples collected at both Phase 3 and Phase 5 were selected via blocked random sampling to ensure an approximately equal number of male and female participants from each study center. Because the remaining blood sample volume was inadequate for 25 samples collected during Phase 3, only 125 of these 150 participants had blood lead measured in whole blood at Phase 3. For an additional sub-study conducted by the Centers for Disease Control and Prevention (CDC), 2,014

participants with sufficient volume of blood sample available at Phase 3 were selected to study blood metals and cardiovascular disease. Among those, 176 participants also had blood samples with sufficient quantity at Phase 5. We combined participants from both sub-studies (N=125 and N=176, with 16 overlapping participants who were included in both sub-studies), for a total of 285 participants with blood lead measurements from both Phase 3 and Phase 5 for the current analysis. The 16 participants with blood metals measured by both sub-studies allowed for direct comparison of both laboratories, i.e., Columbia University Trace Metals Core Laboratory and the laboratory at CDC's National Center for Environmental Health.

Blood lead measurements

In both sub-studies, whole blood samples from Phase 3 and Phase 5 were shipped from Medstar Health Research Institute in Hyattsville, MD on dry ice to their respectivelaboratory, where samples were stored at -80ºC before analysis, and blood lead was measured via inductively coupled plasma-mass spectrometry with dynamic reaction cell (ICP-MS-DRC). The limit of detection was 0.04 µg/dL at the Columbia University Laboratory and 0.049 µg/dL at the CDC laboratory, and no values were measured below the limit of detection at either laboratory. Using blood metal measurements for a total of 32 samples (N=16 participants) included in both sub-studies, we evaluated agreement in measured blood lead concentrations between the two laboratories using linear regression, scatterplots, and Bland-Altman plots (Tukey mean difference). We found no evidence of systematic differences between the two laboratories (Bland Altman bias = 0.02 (95% CI: -0.16, 0.20), regression coefficient 1.05 (95% CI: 0.87, 1.23) (**Supplemental Figures 1 and 2**) and proceeded by pooling all blood lead measurements together.

Blood pressure and echocardiographic measures of cardiac geometry and functioning

Centrally trained SHS nurses and medical assistants measured systolic and diastolic blood pressure (mmHg, averaging three measurements) during physical examinations, as previously described in detail (Lee et al. 1990; North et al. 2003). We defined hypertension as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or reported use of antihypertensive medication. Prehypertension was defined as systolic blood pressure ≥ 120 mmHg or diastolic blood pressure ≥ 80 mmHg.

Expert sonographers performed transthoracic echocardiograms on participants during the Phase 4 (2001-2003) and Phase 5 (2006-2009) study visits, according to standardized and previously described methods (R. B. Devereux et al. 1997). Briefly, echocardiograms were reviewed by two readers and approximately 97% of echocardiograms were finally interpreted by a single highly experienced investigator as recommended by the American Society of Echocardiography (Schiller et al. 1989). Cardiac geometry and functioning were assessed by phased-array echocardiographs with M-mode, 2-dimensional and Doppler capabilities. At least 10 consecutive beats of 2-dimensional and M-mode recordings of cardiac geometry parameters were recorded in the parasternal acoustic window at or just below the tips of the mitral leaflets in both long and short-axis views. The following parameters of cardiac geometry were assessed: left atrium diameter in systole, left ventricular (LV) internal diameter, interventricular septum, LV posterior wall thickness, and relative wall thickness (all measured at end of diastole), and LV mass (calculated by a necropsy-validated formula and normalized for body surface area (de Simone et al. 2005; Devereux et al. 1986)). Midwall shortening was derived as the ratio of midwall fractional shortening (calculated from LV internal dimensions and shell thickness at

diastole and systole) divided by midwall fractional shortening as calculated from a previously established formula including circumferential end-systolic stress (cESS)(De Simone et al. 1994; Schussheim et al. 1998). The parameters of cardiac systolic functioning assessed included ejection fraction (calculated from LV linear dimensions (Devereux et al. 2003)) and stroke volume (via Doppler (Richard B Devereux et al. 1997)). The following parameters of cardiac diastolic functioning were assessed: transmitral early (E) and late (A) filling velocities (measured at the annular level), early peak rapid filling velocity to peak atrial filling velocity (measured as the E/A ratio), deceleration time of early diastolic LV filing, atrial filling fraction, and isovolumic relaxation time (measured between aortic valve closure and mitral valve opening). Because of the small sample size, we did not assess categorical or binary outcomes (e.g. LV hypertrophy, hypertension, etc.).

Other variables

Centrally trained SHS nurses and medical assistants collected participant information from a standardized interview, physical examination, medication review, and biospecimen collection at each study visit. Sociodemographic and lifestyle information was collected from standardized SHS questionnaires, including age, sex, years of schooling/education, whether household income met needs (“yes”/ “no” or “unsure”), exposure to secondhand smoke (hours per week), smoking status (never/ former/ current), and alcohol drinking status (never/ former/ current). Never smoking was defined as reporting never smoking regularly, or never smoking more than 100 cigarettes in lifetime; former smoking was defined as smoking at least 100 cigarettes in lifetime, but not smoking currently; current smoking was defined as smoking at least 100 cigarettes in lifetime and currently smoking. Never drinking was defined as never consuming alcoholic beverages; former drinking was defined as previously consuming alcoholic

beverages, but not within the past 12 months; current drinking was defined as having consumed an alcoholic beverage in the past 12 months.

Detailed methods on the collection of anthropometric measurements and biospecimens (e.g. blood, urine), and the laboratory measurements of relevant biomarkers in biospecimens have been described previously (North et al. 2003) (Lee et al. 1990; Strong Heart Study Coordinating Committee 2001). We calculated estimated glomerular filtration rate (eGFR) using age, sex, and urinary creatinine (mg/dL) via the Chronic Kidney Disease – Epidemiology Collaboration formula (CKD-Epi) (Levey et al., 2009). We defined dyslipidemia as total cholesterol ≥ 200 mg/dL, low density lipoprotein ≥ 130 mg/dL, high density lipoprotein ≤ 40 mg/dL, total triglycerides ≥ 150 mg/dL, or reported use of medication. Impaired fasting glucose was defined as fasting blood glucose ≥ 110 and <126 mg/dL; normal fasting glucose was defined as fasting blood glucose <110 mg/dL.

Statistical analysis

All analyses were conducted in R version 4.1.1. The decline in blood lead concentrations (Phase 5 blood lead concentration minus Phase 3 blood lead concentration) was normally distributed and modeled in the original scale. We first compared baseline (Phase 3) participant characteristics overall and stratified by tertile of decline in blood lead. We then calculated the Spearman correlation coefficients between decline in blood lead (from Phase 3 to Phase 5) and change in systolic blood pressure, diastolic blood pressure, and other metrics of cardiac geometry and functioning (from Phase 4 to Phase 5). We next evaluated the mean change in systolic blood pressure and other metrics of cardiac geometry and functioning per decline in blood lead concentration corresponding to the interquartile range (0.94 µg/dL) in linear generalized

estimating equation (GEE) models to account for the clustering of participants within families. All model adjustment variables were measured at Phase 3 (baseline). Model 1 was adjusted for age, sex, study center, body mass index, and education (<12 years /≥ 12 years). Model 2 was further adjusted for smoking status (never/former/current) and eGFR. Model 3 (the main model of interest) was further adjusted for hypertension treatment/medication use, and baseline systolic blood pressure (in models evaluating the change in diastolic blood pressure, we instead adjusted for baseline diastolic blood pressure). Finally, Model 4 further adjusted for fasting glucose and dyslipidemia. To evaluate the potential dose response relationship, we repeated these analyses evaluating the mean change in outcomes across tertiles of decline in blood lead (with the first tertile as the reference) using GEE models. Finally, we used flexible natural cubic spline models to evaluate potential nonlinearity in the associations between decline in blood lead and blood pressure, cardiac geometry, and cardiac functioning. We included knots at the 50th and 90th percentiles of the decline in blood lead distribution, and set the reference to the 10th percentile.

To further evaluate the impact of interlaboratory measurement agreement on our findings, we repeated our analysis of the mean difference in systolic and diastolic blood pressure per decline in blood lead corresponding to the interquartile range, restricted to blood lead measurements taken at Columbia University (N=125). We also repeated our flexible spline analyses evaluating the change in systolic and diastolic blood pressure measured from Phase 3 to Phase 5 (rather than from Phase 4 to Phase 5). We did not perform stratified subgroup analyses given the small sample size and exploratory nature of the pilot sub-studies.

RESULTS

A total of 285 participants had blood lead measured at both Phase 3 and Phase 5 and were

included in our analyses. Participant characteristics stratified by tertile of decline in blood lead are presented in **Table 1**. For all participants, mean blood lead was 2.04 µg/dL at Phase 3 (baseline). Mean baseline blood lead concentrations were 1.33 µg/dL for participants in the lowest tertile of decline in blood lead and 3.21 µg/dL for participants in the highest tertile of decline in blood lead. Declines in blood lead from Phase 3 to Phase 5 ranged from 7.58 µg/dL to -5.26 µg/dL (negative values represent an increase in blood lead), with those in the highest tertile of decline in blood lead (> 0.88 µg/dL) experiencing a mean decline of 1.78 µg/dL over time. At baseline, 32.9% of participants (n=93) had hypertension and 71.0% had prehypertension (n=201). Participants in the highest tertile of decline in blood lead were more likely to be male, were less likely to have hypertension or prehypertension at baseline, and had lower fasting glucose levels at baseline. The Spearman correlation between decline in blood lead and change in outcomes was only significant for the change in systolic blood pressure (rho = -0.12, $p<0.05$) (**Supplemental Figure 3, Supplemental Figure 4**).

Declines in blood lead from Phase 3 to Phase 5 were associated with declines in systolic blood pressure from Phase 4 to Phase 5 (**Table 2**). In the main model of interest (Model 3), the mean difference in the change in systolic blood pressure comparing participants in the highest tertile of decline in blood lead (>0.88 µg/dL) to those in the lowest tertile of decline in blood lead (<0.27 µg/dL) was -7.08 mmHg (95% CI -13.16, -1.00), representing a decline. The magnitude of this effect estimate increased after further adjustment for baseline fasting glucose and dyslipidemia (Model 4, mean difference -8.17 mmHg, 95% CI -14.59, -1.75). In linear models, a decline in blood lead corresponding to the interquartile range (0.94 µg/dL) was associated with a non-significant mean change in systolic blood pressure of -2.15 mmHg (95% CI -4.45, 0.15) (Model 3). However, declines in blood lead were not linearly associated with mean difference in

systolic and diastolic blood pressure in flexible cubic spline models (**Figure 1**). Associations were null and flat when there was no decline and became apparent when declines in blood pressure exceeded 0.1 µg/dL. Similar to our findings from tertile models, in flexible spline models the association between decline in blood lead and the mean difference in systolic blood pressure was statistically significant and apparent when declines in blood lead were >0.1 µg/dL. Flexible splines modelling declines in blood lead and changes in diastolic pressure followed similar trends, but were not statistically significant. In sensitivity analyses restricting to blood lead measurements taken at the Columbia University Laboratory, effect estimates were similar to those in our main analysis (**Supplemental Table 1**). Associations were attenuated in sensitivity analyses considering changes in blood pressure from Phase 3 to Phase 5 rather than changes from Phase 4 to Phase 5 (**Supplemental Figure 5**).

Flexible spline models of the mean difference in other metrics of cardiac functioning and geometry per decline in blood lead are presented in **Figure 2** and **Figure 3**. Declines in blood lead were significantly associated with declines in midwall shortening (**Figure 2**) and declines in interventricular septum in systole (**Figure 3**). Declines in blood lead were also associated with increases in transmitral early filing velocity (E-velocity, **Figure 2**), but only at the highest ends of the decline in blood lead distribution where the sample size was very small.

DISCUSSION

This study evaluates the impact of blood lead declines on blood pressure and measures of left ventricular geometry and functioning, is the first to examine short-term changes in an American Indian population, and is one of the few longitudinal studies of changes in blood pressure levels conducted at low levels of lead exposure. In a sample of SHFS participants,

declines in blood lead were associated with marked decreases in systolic blood pressure. The relationship between declines in blood lead and systolic blood pressure was non-linear, with statistically significant reductions in systolic blood pressure observed after lead declines greater than 0.1 μg/dL. The association of declines in blood lead with changes in diastolic blood pressure were non-statistically significant. Declines in blood lead were associated with non-linear and non-significant changes in measures of cardiac geometry and functioning, including decreases in interventricular septum length in systole and midwall shortening.

These findings reported in an American Indian population are important to integrate within the broader literature. Historically, widespread bans of lead in gasoline in the 1970s, the phasing out of lead-based paint products, and specific policy to reduce exposure within the home were main drivers behind declines in lead exposure in the US (Brown et al. 2001; Development 1992; Dignam et al. 2019; Landrigan and Bellinger 2021) Despite this, lead exposure remains persistent, with evidence of racial and socioeconomic disparities in exposure (Lanphear et al. 1996; Moody et al. 2016; Anne E Nigra and Ana Navas-Acien 2021), and exposure also occurring through drinking water distribution systems, herbal supplements, and tobacco products (Buettner et al. 2009; Maas et al. 2005; Mannino et al. 2005; Santucci Jr and Scully 2020). In this study, blood lead levels reported here were similar in magnitude to those reported across the general US population, although North Dakota/South Dakota participants had the higher blood lead levels at baseline (mean: 2.25, sd: 1.45 μg/dL). As compared to median blood lead concentrations among adults 50 years and older in NHANES 1999-2000 (2.17 [95% CI: 2.08–2.26] μg/dL), concentrations measured in this sample (mean: 2.04, sd: 1.32 μg/dL) at Phase 3 (1997-1999) were similar. Research has identified that across NHANES data from 1988-1994

and 1999-2002, the geometric mean of blood lead levels declined from 2.76 µg/dL (0.13 µmol/L) in 1988-1994 to 1.64 µg/dL (0.08 µmol/L) in 1999-2002 (Muntner et al. 2005). While the study time periods are not directly comparable, the present analysis reports that declines in blood lead are lesser (mean: 0.67, sd: 1.19 µg/dL) in this sample of American Indians. This finding could reflect the persistent problem and potential disproportionate exposure of lead in American Indians compared to the general population (Agency 2020; Hoover et al. 2012; Pang et al. 2016). This exposure could stem from drinking water, as lead within Northern Plains tribal communities has been documented in both private and public water systems (Bradley et al. 2022). Additionally these findings draws attention to the notion that reductions in lead among American Indian communities with potentially elevated exposure can have profound reductions in blood pressure and changes in cardiovascular health in this population.

The current study complements available evidence on the relationships between blood lead and blood pressure reported in the general US population. Prior analyses from NHANES-II (1976 to 1980) have observed statistically significant positive relationships between blood lead and blood pressure in men after adjustment, where blood lead levels were ~16 µg/dL (Harlan 1988; Pirkle et al. 1985). This relationship has also been observed among black men and women specifically in NHANES 1988-1994 at lower blood lead concentrations of ~5 µg/dL (Vupputuri et al. 2003). More recent NHANES data from 1999-2016, where blood lead was < 5 µg/dL, has also also documented increasing blood lead with an increased risk of hypertension (Tsoi et al. 2021). The positive relationship blood lead and both systolic and diastolic blood pressure has also been noted in international occupational cohort studies (Kim et al. 2020; Lu et al. 2015; Nomiyama et al. 2002), although limited evidence exists from US occupational cohorts (Yu et al. 2020). The

findings reported here at blood lead concentrations of ~ 2 µg/dL provide important evidence of the benefits of reducing blood lead even at these lower levels, and are the first from a cohort American Indians. Further, the observed reductions in systolic blood pressure reported here are consistent regarding established links between chronic lead exposure and the promotion of oxidative stress, endothelial injury, alterations of the renin-angiotensin system, inflammation, arteriosclerosis, atherosclerosis, and thrombosis(Vaziri 2008). The present analysis reports that relationships between blood lead declines and blood pressure were attenuated in analyses considering changes in blood pressure from a longer period of time (Phase 3 to Phase 5), compared to changes occurring from Phase 4 to Phase 5. This finding could potentially reflect some latency in the physiologic action of lead on the vascular system.

This analysis builds on prior research on metals exposure and cardiovascular disease from across the broader literature and within the SHS. Previous findings from the SHFS have identified the impact of increasing urinary arsenic concentrations on increases in left ventricular wall thickness and left ventricular hypertrophy (Pichler et al. 2019). This study also reported a more pronounced effect of arsenic among individuals with either prehypertension or hypertension, emphasizing the impacts and vulnerability of those with elevated blood pressure to exposure to environmental toxicants. Notably, this prior analysis was performed on a larger sample of SHFS participants (n=1337), both free of diabetes and cardiovascular disease at baseline, and the sample size of the present study prevented investigation of cardiovascular measures by hypertensive status. Comparatively however, the study population of the current analysis was similar in terms of gender, BMI, and smoking status, albeit with a slightly older age. Despite investigating the impact of two different metals, arsenic and lead and Pb, the results presented in

the current analysis identify the profound impact of reducing blood lead on blood pressure, with implications for cardiovascular health. While prior research in the SHS has identified that participants in North Dakota/South Dakota have higher blood lead levels (Li et al. 2022), we report here that all centers showed declines in blood lead over the study period. Limitations in sample size, however, prevented investigating trends by study center of recruitment in fully adjusted analyses. The reported associations between lead and blood pressure and the reductions in lead exposure observed in our population could help explain improvements in cardiovascular morbidity and mortality across the entire SHS (Muller et al. 2019).

While subclinical measures of cardiac geometry and functioning have previously been studied in the SHFS, further research is needed to determine the impact of lead on these subclinical outcomes across different study populations. Findings from the general US population utilizing NHANES data have reported increases in blood lead related to subclinical myocardial injury (Wang et al. 2022). Various studies performed in occupational populations have also identified a variety of cardiovascular measures associated with blood lead (Navas-Acien et al. 2007), including increased prevalence of left ventricular hypertrophy (Schwartz 1991), left ventricular mass, and lower ejection fraction (Kasperczyk et al. 2005). While the current study identified reductions in blood lead with decreases in interventricular septum length in systole and midwall shortening, it is essential to not only study the relationship of lead with cardiovascular outcomes in a larger American Indian population, but to investigate the impact of multiple metals simultaneously on these subclinical outcomes(Pang et al. 2016).

One limitation of this analysis is that lead was only measured in a relatively small sample of SHFS participants (N=285). A larger sample could help underscore the relationship between declines in blood lead and blood pressure across the entire SHFS, in particular by evaluating associations across subgroups by study center, sex, age groups, diabetes status and other characteristics. For instance, the Trial to Assess Chelation Therapy found a stronger cardiovascular benefit for a chelating agent that primarily removes lead from the body among participants with a prior myocardial infarction who also had diabetes (Lamas et al. 2013; Lamas et al. 2016; Ouyang et al. 2015). Whether the blood pressure benefit from declines in lead exposure observed in this study are also larger among participants with diabetes could not be evaluated due to the small sample size. The small sample size could also explain the absence of statistically significant relationships between blood lead declines and changes in measures of cardiac functioning and structure, as well as diastolic blood pressure levels. The weaker association between lead and diastolic blood pressure compared to systolic blood pressure has been reported before and likely requires larger sample sizes (Agency 2006; Hertz-Picciotto and Croft 1993; Navas-Acien et al. 2007; Schwartz 1995). In the absence of traditional lead measures assessed in blood or urine, prior research across the SHS has utilized epigenetic biomarkers of lead exposure as a surrogate for lead exposure. Using those DNA-methylation data to generate an estimate of lead exposure, we observed an association between estimates of blood lead and cardiovascular disease mortality, consistent with the findings between blood lead and blood pressure reported in this study.

Conclusion

In a sample of SHFS participants, declines in blood lead levels occurring between 1997-1999 and 2006-2009 were associated with marked reductions in systolic blood pressure levels and with specific measures of cardiac geometry and functioning. These results, obtained at a time when lead exposure was already relatively low in the SHFS, consistent with other US populations, further highlights the important vascular benefits of reducing lead exposure in both American Indian populations and the general US population.

TABLES

Table 1. Participant characteristics at Phase 3 (1997-1999), stratified by tertile of decline in blood lead (µg/dL) from Phase 3 (1997-1999) to Phase 5 (2006-2009) (N=285). Tertile 1 represents the smallest blood lead decline (<0.27 µg/dL decline), and tertile 3 represents the largest blood lead decline (>0.88 µg/dL decline). Negative values of the decline in blood lead represent increases in blood lead over time.

	Overall -5.26 – 7.58 µg/dL decline	**Tertile 1 < 0.27 µg/dL decline**	**Tertile 2 0.27 – 0.88 µg/dL decline**	**Tertile 3 > 0.88 µg/dL decline**	**P value**	**n**
Blood lead (µg/dL) at Phase 3 (baseline), mean (SD)	2.04 (1.32)	1.33 (0.64)	1.58 (0.65)	3.21 (1.52)		
Decline in blood lead (µg/dL), mean (SD)	0.67 (1.19)	-0.33 (0.89)	0.55 (0.18)	1.78 (1.06)		
N (%)	285 (100)	95 (33.3)	95 (33.3)	95 (33.3)		
Center, n (%):						
Arizona	39 (13.7)	16 (16.8)	15 (15.8)	8 (8.4)	0.398	285
Oklahoma	146 (51.2)	47 (49.5)	50 (52.6)	49 (51.6)		
North & South Dakota	100 (35.1)	32 (33.7)	30 (31.6)	38 (40.0)		
Female, n (%):	170 (59.6)	69 (72.6)	58 (61.1)	43 (45.3)	<0.001	285
Age (years), mean (SD)	51.5 (16.3)	52.7 (17.2)	47.7 (16.1)	53.9 (15.2)	0.613	285
Education (years), n (%):						
≥12	111 (38.9)	40 (42.1)	42 (44.2)	29 (30.5)	0.114	285
<12	174 (61.1)	55 (57.9)	53 (55.8)	66 (69.5)		
Income meet needs? n (%):						
Yes	117 (73.6)	37 (69.8)	47 (75.8)	33 (75.0)	0.744	159
No/Unsure	42 (26.4)	16 (30.2)	15 (24.2)	11 (25.0)		
Smoking status, n (%):						
Former	65 (23.0)	20 (21.3)	19 (20.0)	26 (27.6)	0.179	283
Never	123 (43.5)	49 (52.1)	40 (42.1)	34 (36.2)		
Current	95 (33.5)	25 (26.6)	36 (37.9)	34 (36.2)		
Secondhand smoke exposure (hrs/week) mean (SD)	1.9 (3.5)	1.3 (2.4)	2.5 (4.4)	1.9 (3.3)	0.325	158
Alcohol consumption status, n (%):						
Former	114 (40.3)	33 (35.1)	36 (37.9)	45 (47.9)	0.258	283
Never	49 (17.3)	21 (22.3)	14 (14.7)	14 (14.9)		
Current	120 (42.4)	40 (42.6)	45 (47.4)	35 (37.2)		
Body mass index (kg/m^2), mean (SD)	30.8 (6.8)	31.1 (6.4)	31.6 (8.1)	29.8 (5.4)	0.173	282
Hypertension, n (%):	93 (32.9)	41 (43.6)	24 (25.3)	28 (29.8)	0.02	283

Prehypertension, n (%):	201 (71.0)	76 (80.9)	60 (63.2)	65 (69.1)	0.024	283
Hypertension treatment, n (%):	64 (22.5)	32 (33.7)	17 (17.9)	15 (16.0)	0.006	284
Fasting glucose, mean (SD)	113.2 (48.2)	122.4 (56.9)	111.7 (49.2)	105.4 (34.6)	0.015	284
Impaired fasting glucose, n (%):	20 (8.7)	4 (6.1)	10 (12.2)	6 (7.3)	0.361	230
Dyslipidemia, n (%):	197 (78.2)	63 (78.8)	68 (76.4)	66 (79.5)	0.875	252
eGFR (CKD-Epi), mean (SD)	106 (21.8)	103.5 (25.6)	109.5 (20)	105 (19)	0.66	284
Systolic blood pressure, mean (SD)	127.3 (16.2)	130 (16.5)	124.5 (14.8)	127.2 (16.8)	0.241	283
Diastolic blood pressure, mean (SD)	75 (8.7)	74.8 (9.3)	75.7 (8.5)	74.5 (8.2)	0.805	284

Table 2. Mean difference in the change in systolic and diastolic blood pressure (mmHg) from Phase 4 (2001-2003) to Phase 5 (2006-2009) across tertiles of blood lead decline from Phase 3 (1997-1999) to Phase 5 (2006-2009) and by decline in blood lead corresponding to the interquartile range (IQR) (N= 278). Negative values represent declines in blood pressure. Tertile 1 represents the smallest blood lead decline, and tertile 3 represents the largest blood lead decline. Model 1 was adjusted for sex, age, center, body mass index, and education (<12 years/ ≥ 12 years). Model 2 was further adjusted for smoking status (never/former/current) and estimated glomerular filtration rate (calculated via the CKD-Epi formula). Model 3 was further adjusted for hypertension treatment/medication and baseline systolic blood pressure. Model 4 was further adjusted for fasting glucose and dyslipidemia.All model adjustment variables were measured at Phase 3 (baseline).

	Tertile 1 <0.27 µg/dL	**Tertile 2 0.27–0.88 µg/dL**	**Tertile 3 >0.88 µg/dL**	**Per IQR decrease (0.94 µg/dL)**
Systolic blood pressure (SBP)				
Model 1	1 (reference)	-2.13 (-7.00, 2.74)	-6.65 (-12.51, -0.79)	-2.00 (-4.11, 0.12)
Model 2	1 (reference)	-1.78 (-6.68, 3.11)	-6.44 (-12.30, -0.58)	-2.07 (-4.25, 0.11)
Model 3	1 (reference)	-2.51 (-7.38, 2.35)	-7.08 (-13.16, -1.00)	-2.15 (-4.45, 0.15)
Model 4	1 (reference)	-2.48 (-7.66, 2.70)	-8.17 (-14.59, -1.75)	-2.28 (-4.72, 0.16)
Diastolic blood pressure (DBP)				
Model 1	1 (reference)	1.11 (-1.82, 4.04)	-1.06 (-4.15, 2.04)	-0.51 (-1.41, 0.39)
Model 2	1 (reference)	1.35 (-1.58, 4.28)	-0.97 (-4.10, 2.16)	-0.62 (-1.60, 0.36)
Model 3	1 (reference)	1.51 (-1.46, 4.49)	-0.86 (-4.03, 2.31)	-0.59 (-1.59, 0.42)
Model 4	1 (reference)	0.95 (-2.18, 4.08)	-1.87 (-5.38, 1.64)	-0.82 (-1.94, 0.31)

FIGURES AND FIGURE LEGENDS

Figure 1. Restricted cubic spline models of the mean difference in the change in systolic and diastolic blood pressure (mmHg) from Phase 4 (2001-2003) to Phase 5 (2006-2009) by declines in blood lead from Phase 3 (1997-1999) to Phase 5 (2006-2009) (N= 278). Negative values represent declines in blood pressure. Analysis was restricted to N=278 participants without missing covariate data. Models are adjusted for sex, age, study center, body mass index, education (<12 years/≥ 12 years), smoking status (never/former/current), estimated glomerular filtration rate (calculated via the CKD-Epi formula), hypertension medication/treatment, and baseline systolic blood pressure. All model adjustment variables were measured at Phase 3 (baseline). The reference is set to the 10th percentile of the change in decline in blood lead distribution (-0.43 µg/dL), with knots at the 50th and 90th percentiles. Alternative knot placements (50th, 75th percentiles) yielded similar findings.

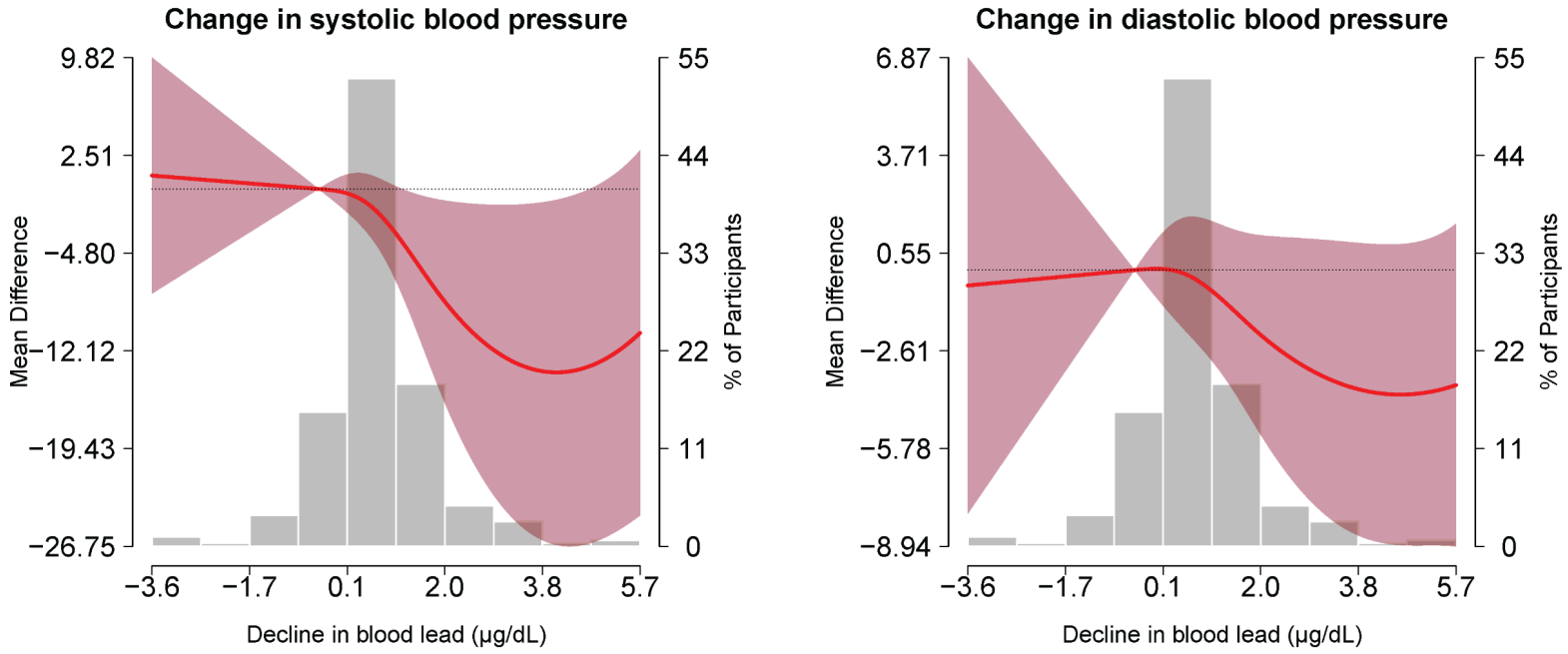


Figure 2. Restricted cubic spline models of the mean difference in the change in cardiac functioning measures from Phase 4 (2001-2003) to Phase 5 (2006-2009) by declines in blood lead from Phase 3 (1997-1999) to Phase 5 (2006-2009) (N= 78). Models are adjusted for sex, age, study center, body mass index, education (<12 years/≥ 12 years), smoking status (never/former/current), estimated glomerular filtration rate (calculated via the CKD-Epi formula), hypertension medication/treatment, and baseline systolic blood pressure. All model adjustment variables were measured at Phase 3 (baseline). The reference is set to the 10th percentile of the change in blood lead distribution (-0.43 µg/dL), with knots at the 50th and 90th percentiles. Alternative knot placements (50th, 75th percentiles) yielded similar findings.

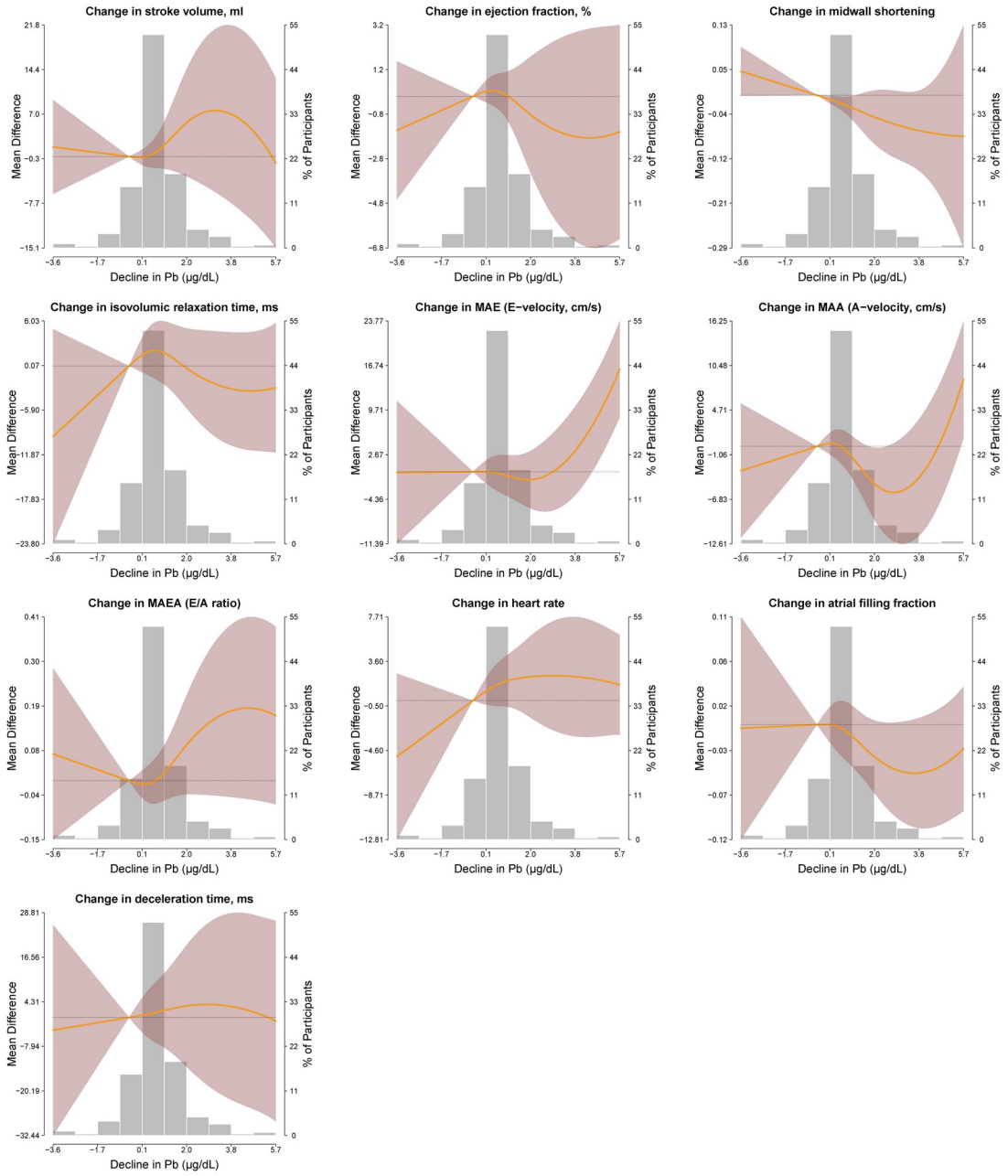
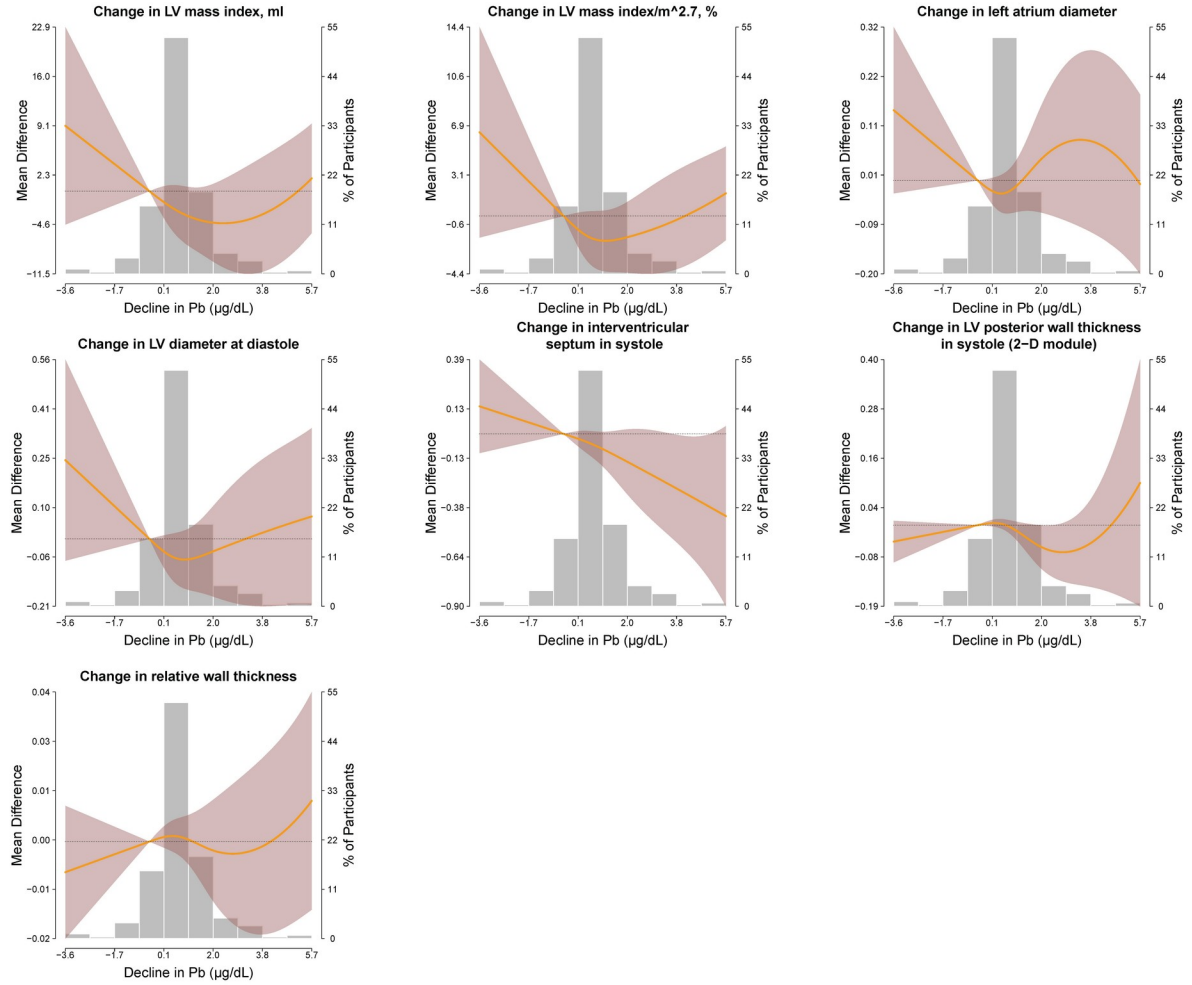


Figure 3. Restricted cubic spline models of the mean difference in the change in cardiac geometry measures from Phase 4 (2001-2003) to Phase 5 (2006-2009) by declines in blood lead from Phase 3 (1997-1999) to Phase 5 (2006-2009) (N= 278). Models are adjusted for sex, age, study center, body mass index, education (<12 years/≥ 12 years), smoking status (never/former/current), estimated glomerular filtration rate (calculated via the CKD-Epi formula), hypertension medication/treatment, and baseline systolic blood pressure. All model adjustment variables were measured at Phase 3 (baseline). The reference is set to the 10th percentile of the change in blood lead distribution (-0.43 µg/dL), with knots at the 50th and 90th percentiles. Alternative knot placements (50th, 75th percentiles) yielded similar findings.



Availability of data and material:

Strong Heart Study data is owned by the participating tribes and is not available for public use.

Competing interests:

The authors declare that they have no actual or potential competing financial interests.

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