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Article

The Association of Blood Lead with Cardiovascular Disease Incidence and Mortality: Findings from the Strong Heart Study Cohort

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ABSTRACT: **BACKGROUND**: Evidence on lead and the burden of cardiovascular disease (CVD) derived from National Health and Nutrition Examination Survey (NHANES) data, a general sample of the U.S. population, lacks sufficient representation of American Indians. Moreover, there is limited prospective evidence of lead and incident CVD outcomes. **OBJECTIVES**: We evaluated whether blood lead levels were associated with CVD mortality and incidence in American Indian adults from the Strong Heart Study (SHS). **METHODS**: Whole blood samples collected in 1998−1999 among 1,818 participants were analyzed for lead using inductively coupled plasma mass spectrometry. CVD incidence and mortality data were available through 2019. We used progressively adjusted multivariable Cox proportional hazards models to estimate the risk of composite CVD and coronary heart disease (CHD) mortality and incidence by baseline blood lead levels. **RESULTS**: The median (p20, p80) blood lead was 22.5 (14.2, 37.3) μg/L, similar to that of a representative sample of U.S. adults in NHANES 1999−2000. During follow-up, 578 (31.8%) participants had a composite CVD event, and 454 (25.0%) participants had a CHD event. After adjustment for demographics, lifestyle, and cardiovascular risk factors, the hazard ratio (95% CI) per change across the 80th to 20th quantiles in blood lead was 1.15 (1.02−1.30) and 1.22 (1.08−1.37) for CVD and CHD mortality, respectively, and 1.13 (1.02−1.24) and 1.12 (0.99−1.25) for CVD and CHD incidence, respectively. In flexible dose−response models, the associations appeared to be nonlinear, with a clear increased risk of CVD and CHD mortality at blood lead concentrations above 35 μg/L. **DISCUSSION**: Blood lead levels in American Indian adults, which are comparable to populations in the U.S. and globally, were associated with an increased risk of CVD and CHD incidence and mortality. These findings highlight the importance of further reducing lead exposure, including American Indian communities.

INTRODUCTION

Chronic lead poisoning was recognized to induce atherosclerosis more than a century ago in autopsy studies and clinical manuals.[1,2] Despite well-known toxicity to multiple organs and systems, lead exposures increased greatly in the 20th century with ubiquitous use of lead-based paint and plumbing fixtures as well as the addition of tetraethyl lead to gasoline. Lead is a divalent cation that interferes with the essential metals calcium and zinc and is associated with adverse cardiovascular and other health outcomes,[3−6] possibly related to promoting oxidative stress, vascular reactivity, epigenetic changes, and other mechanisms.[7−10] This results in increased inflammation and the development of atherosclerosis.[10] Multiple studies of participants recruited in the National Health and Nutrition Examination Survey (NHANES) from 1976 through 2012 indicate that widespread lead exposure has been a major risk factor contributing to the burden of cardiovascular disease (CVD) in the United States.[5,11−16] These studies using NHANES, together with evidence from other populations[17−24] and experimental and mechanistic evidence,[7−10] formed the basis for the US Environmental Protection Agency (US-EPA)[8] and the American Heart Association[25] to recognize chronic lead exposure as a CVD risk factor.

Globally, risk assessment analyses have estimated that over 5.5 million CVD deaths in 2019 were attributed to environmental lead exposure.[26] Most of the studies on the association between lead and CVD risk were conducted decades ago, when few participants had blood lead levels below 35 μg/L (3.5 μg/dL). This level is the current blood lead reference value for U.S. children ages 1−5 years from the Centers for Disease Control Prevention (CDC),[27] as well as the reference value used by the Council of State and Territorial Epidemiologists (CSTE)[28] and California Department of Public Health (CDPH)[29] for management, repeated testing, and clinical action in adults. This level is important to consider for populations in the US and in many countries globally[30]

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with respect to the health effects. Of note, the National Institute for Occupational Safety and Health (NIOSH) uses a blood lead level of 50 μg/L (5 μg/dL) in adults for surveillance purposes. Following the introduction of legislation and guidelines to reduce lead exposure, levels have declined, and studies in populations exposed to currently relevant levels of lead are needed to understand the role of lead exposure in CVD. Additionally, there is need to study lead-CVD associations in populations with risk factor profiles different from those represented in NHANES.

The Strong Heart Study (SHS) is a population-based prospective cohort study of CVD and its risk factors in American Indian adults across the U.S. Southwest and the Great Plains.[31] Blood lead levels in SHS participants measured in samples collected in 1998−1999 (median 22.5 μg/L) were similar to those found in a representative sample of U.S. adults in NHANES 1999−2000 (median 20 μg/L).[32] Previous work identified that blood lead levels in the SHS fall across a broad range (3.13−506.6 μg/L), representing a unique opportunity to investigate the association of blood lead with CVD incidence and mortality at levels typical of many populations in the U.S. and worldwide.[32] American Indian populations have an elevated burden of clinical and behavioral CVD risk factors (e.g., diabetes mellitus, smoking, and physical activity), and their social determinants of health (e.g., poverty, educational attainment, and access to health insurance) differ from those across the general U.S. population.[33] We hypothesized that blood lead levels are associated with adverse cardiovascular outcomes with a monotonic dose−response and no evidence of a threshold, although a decelerating dose−response is also possible. We hypothesized that associations with CVD would be driven by coronary heart disease (CHD), based on prior evidence available from NHANES for CHD mortality.

METHODS

Study Population

The SHS is a community-based participatory research prospective cohort study of CVD working in partnership with tribal communities in the U.S. Southwest and the Great Plains.[31] In 1989−1991, all adults aged 45−74 years in the communities in Arizona and Oklahoma, and random subsets in the communities in North Dakota and South Dakota, were eligible for recruitment.[31] Every eligible person was invited to participate in Arizona and Oklahoma, whereas a cluster sampling technique was used in the center in North Dakota and South Dakota.[31] The protocol was approved by academic institutional review boards (IRBs), participating tribal communities, their research review boards, and the respective area Indian Health Service IRBs. All participants provided their informed consent. This article has been reviewed by the participating communities. The data used in this analysis cannot be shared publicly in an unrestricted manner due to limitations in the consent forms and in the agreements between the SHS tribal communities and the SHS investigators. The data can be shared to external investigators following the procedures established by the SHS, available at https://strongheartstudy.org/. This analysis used the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines.[34]

A total of 4,549 adults were initially recruited in 1989−1991, and participation rates were 72%, 62%, and 55% for the Arizona, Oklahoma, and North/South Dakota study centers, respectively (62% overall).[35] We excluded 1,036 participants among one community that declined further participation. Whole blood lead was measured among 2,196 men and women who participated in the third physical exam in 1998−1999, which serves as baseline visit for this study. Each participant had a single venous blood draw performed by certified examiners, and vials for blood collection were not checked for lead contamination. Those with prior CVD at the baseline were not excluded to maximize power and to consider new events. We excluded 188 participants with clotted blood samples and 2 with an insufficient blood sample available for lead analysis. We also excluded 188 participants missing information on covariates and CVD risk factors, such as body mass index, smoking status, and blood pressure, resulting in a final sample size of 1,818 participants in this study.

As described previously,[31,36] all participants provided sociodemographic and medical history information, including age, sex, education, field center, smoking status (never, former, current), body mass index (BMI), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), blood pressure, hypertension treatment (yes/no), and diabetes (yes/no) via baseline questionnaires, physical exams, and laboratory assays. Estimated glomerular filtration rate (eGFR) was calculated using age, sex, and plasma creatinine via the Chronic Kidney Disease−Epidemiology Collaboration formula.[37] Diabetes status at baseline was defined as fasting glucose ≥126 mg/dL, two h plasma glucose ≥200 mg/dL, hemoglobin A1C level ≥6.5%, self-reported history of diagnosis, or current use of diabetic medication. For the glucose tolerance test, blood samples were drawn by venipuncture at fasting and at 2 h after ingestion of a 75 g glucose load (Glutol, Paddock Laboratory, Inc., Minneapolis, MN).[31] Plasma creatinine measurements are determined by enzymatic methods using reagent kits from Boehringer Mannheim Diagnostic (Indianapolis, IN) on a chemistry analyzer.[31]

Blood Lead Measurement

Aliquots of whole blood samples were stored at ≤70 °C, and frozen whole blood samples were shipped on dry ice to CDC in 2019 and processed as described previously.[32] Lead and cadmium were measured using inductively coupled plasma triple quadrupole mass spectrometry (ICP-QQQ-MS).[38] Specifically, a 50 μL aliquot of whole blood was diluted to 1 mL in an aqueous solution of 1.0% (v/v) tetramethylammonia hydroxide, 1% (v/v) ethanol, 0.01% (v/v) ammonium pyrrolidine dithiocarbamate (APDC), 0.05% (v/v) Triton X-100, and a 5 μg/L iridium internal standard. The sample mixture was then analyzed using the Agilent 8900 ICP-QQQ-MS. Lead (^{206}Pb + ^{207}Pb + ^{208}Pb), cadmium (^{111}Cd), and the internal standard iridium (^{193}Ir) were all analyzed within a single tune mode where the octopole reaction cell was pressurized with 50% oxygen and 1.0 mL/min hydrogen. Quantitation was achieved using a matrix-matched, external calibration with calibration ranges of 0.6−2000 μg/L for lead and 0.06−200 μg/L for cadmium. The limits of detection were 0.49 μg/L for lead and 0.065 μg/L for cadmium. One sample was below the limit of detection (LOD) for cadmium and was replaced with the LOD divided by the square root of two. Three custom-made blood bench quality control (QC) materials were inserted into the beginning and end of each analytical run. QC checks were performed according to a multirule quality control system.[39] The laboratory also conducted quarterly checks of the method accuracy against standard reference materials from the National Institute of Standards and Technology (NIST) and participated in an external proficiency testing program. QC results are given in Table S1. We report blood lead in μg/L rather than traditional units of μg/dL following recent calls to improve perception around "safe" levels, communication, and comparisons with other contaminants.[40]

Cardiovascular Outcomes

Morbidity and mortality surveillance in the SHS is ongoing and has been previously described.[41,42] All cardiovascular disease outcomes and deaths are identified through coordination among the SHS Field Centers, the SHS Coordinating Center, and Surveillance Reporting. The SHS used questionnaire, physical examinations, and laboratory data obtained during study visits, as well as tribal records, Indian Health Service hospital records, death certificates, and direct annual contact with participants and their families to assess the study end points at baseline and during follow-up. Incident cardiovascular end points during follow-up were identified by annual contact, review of hospitalization and death records, and clinic visits. When possible cardiovascular events were identified, medical records were abstracted,

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and Mortality and Morbidity Review Committees adjudicated cardiovascular events. For this study, all deaths and potential cardiovascular outcomes occurring through 2019 were reviewed by the Morbidity and Mortality Review Committee, which is composed of physicians with experience in reviewing medical records for the ascertainment of cardiovascular outcomes.[41,42] Incident CVD was defined as any definite or possible fatal or nonfatal CHD, stroke, or heart failure. Definite CHD was based on the following criteria: (a) cardiac cath proven coronary artery disease (1 or more vessels ≥50% stenosis), (b) percutaneous transluminal coronary angioplasty (PTCA), (c) coronary artery bypass grafting, (d1) abnormal stress electrocardiogram, (d2) abnormal imaging, or (e) positive functional test of ischemia (such as treadmill). Possible CHD was defined as participants with some, but not all, criteria or with equivocal criteria for definite CHD. For possible fatal CHD, the criteria are (1) documentation by criteria of definite acute myocardial infarction (MI) within 4 weeks prior to death and (2) no documentation by criteria of definite sudden death, and (3) no documentation by criteria of definite fatal CHD, and (4) death certificate with consistent underlying or immediate cause (ICD-9 codes 410−414) and (5) no known atherosclerotic or nonatherosclerotic process that was probably lethal according to the death certificate, autopsy report, hospital records, or physician records. Definite fatal CHD and possible fatal CHD are defined in the Supporting Information.

Criteria used for ascertaining the primary CVD deaths are the International Diagnostic criteria for acute MI and acute stroke and the criteria for fatal congestive heart failure (CHF) of the Framingham study. Events possibly meeting these criteria included definite fatal MI, definite sudden death due to CHD, definite fatal CHD, possible fatal CHD, definite fatal stroke, possible fatal stroke, definite fatal CHF, possible fatal CHF, and other fatal CVD.

Statistical Analysis

Blood lead levels were stratified by demographic and clinical covariates to characterize differences across participant characteristics. In main analyses we used progressively adjusted multivariable Cox proportional hazards models to estimate the risk of composite CVD mortality and CVD incidence, as well as CHD mortality and CHD incidence by baseline blood lead levels. To comprehensively assess the shape of the dose−response, lead was categorized into policy-relevant cutoffs (≤10.0 [lowest category], >10.0−35.0, >35.0 μg/L) and also evaluated continuously in the original scale for a change across the 80th to 20th quantiles (14.2−37.3 μg/L) of lead, as well as in a flexible manner using restricted quadratic splines on log-transformed blood lead levels, with knots at the 10th, 50th, and 90th percentiles and the reference at the 10th percentile. Lead levels ≤10.0 μg/L capture current average blood lead levels in the U.S. population (2010-onward).[43] In all Cox models, the field center was incorporated as a strata term, and age was used as the time metric. Model 1 (adjusted for sex, smoking status (never/former/current), BMI (kg/m^2), and eGFR (mL/min/1.73 m^2)) includes known determinants of CVD that are related to blood lead levels.[44,45] Model 2 was further adjusted for LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), diabetes status (yes/no), systolic blood pressure (mmHg), and hypertension treatment (yes/no) at baseline. This model incorporates additional traditional risk factors for CVD. Model 3 was further adjusted for blood cadmium, which is correlated with blood lead and is also related to CVD risk.[5,20,25] Sensitivity analyses were performed by modeling blood lead in tertiles, modeling policy relevant groupings of blood lead with the middle grouping as the reference, with additional adjustment for socioeconomic characteristics (years of educational attainment, household income), removing adjustment for eGFR, hypertension, and systolic blood pressure, removing participants with outliers in blood lead, and censoring follow-up at 90 years and older of age.

Moderation of the relationship between blood lead and CVD mortality and incidence was investigated according to the following subgroups: age at baseline (44.0−49.9, 55.0−64.9, 65.0−75.4 years), sex (male/female), study center (Arizona, Oklahoma, North Dakota/South Dakota), smoking status (never/former/current), BMI (<25, ≥25 to <30, ≥30 kg/m^2), diabetes status (yes/no), and tertiles of blood cadmium levels (<0.44, 0.44−0.84, >0.84 μg/L). Cox proportional hazards models for each end point included interaction terms between the subgroup and blood lead levels to estimate the p-values for interaction. We also report an increase in the change across the 80th to 20th quantiles of blood lead, modeled in the original scale, for each subgroup. Interaction models were performed for descriptive purposes to evaluate if the associations were consistent across subgroups. All analyses were conducted in R version 4.0.2.[46]

RESULTS

The mean (SD) age of participants at baseline was 63.9 (7.9) years, and 1,110 (61.1%) participants were female. The median (p20, p80) blood lead level was 22.5 (14.2, 37.3) μg/L. Blood lead concentrations followed a log-normal distribution (Figure S1). Blood lead concentrations were higher among males, participants recruited from North Dakota and South Dakota, current smokers, participants without diabetes, and those with an eGFR of <60 mL/min/1.73 m^2 (Table 1).

Over the study follow-up, the median follow-up time was 8.6 years for participants with CVD incident events, 11.0 years for those with CVD deaths, and 18.0 years for those without CVD events. A total of 410 (22.6%) had a fatal CVD event and 578

Table 1. Blood Lead Concentrations by Participant Characteristics (N = 1,818)[a]

			Blood lead (μg/L)
	Variable	N (%)	Median (p20, p80)
Sex	Male	708 (38.9)	28.7 (18.6, 46.3)
	Female	1,110 (61.1)	19.3 (12.5, 31.4)
Age (years)	<55	243 (13.4)	22.4 (14.9, 36.2)
	55−64	848 (46.6)	21.2 (13.5, 36.6)
	≥65	727 (40.0)	23.9 (15.4, 38.4)
Center	AZ	186 (10.2)	15.6 (10.1, 24.5)
	OK	787 (43.3)	20.8 (13.1, 33.7)
	ND/SD	845 (46.5)	26.0 (17.0, 41.8)
Smoking Status	Never	622 (34.2)	19.8 (12.7, 30.6)
	Former	631 (34.7)	21.2 (13.7, 34.0)
	Current	565 (31.1)	28.9 (17.8, 44.2)
BMI	<25 kg/m^2	306 (16.8)	29.9 (17.5, 46.8)
	25−30	604 (33.2)	25.0 (15.7, 39.9)
	≥30	908 (50.0)	19.8 (12.8, 30.9)
Diabetes	Yes	821 (45.2)	19.6 (15.9, 41.9)
	No	997 (54.8)	26.1 (12.9, 30.8)
HT Treatment	Yes	657 (63.9)	21.0 (13.7, 34.6)
	No	1,161 (36.1)	23.6 (14.7, 38.8)
SBP	<129	890 (49.0)	23.4 (14.7, 38.3)
	≥129	928 (51.0)	22.0 (13.7, 36.1)
Household Income	<$10,000	684 (51.6)	25.2 (15.3, 41.9)
	≥$10,000	641 (48.4)	21.3 (14.4, 33.7)
Education	<12 years	590 (32.2)	25.2 (15.5, 42.0)
	≥12 years	1,119 (61.6)	21.2 (13.8, 34.0)
eGFR	<60 mL/min/1.73 m^2	134 (7.4)	29.5 (18.4, 48.8)
	≥60 mL/min/1.73 m^2	1,684 (92.6)	22.1 (14.0, 36.3)

[a]BMI: body mass index. HT: hypertension. eGFR: estimated glomerular filtration rate. SBP: systolic blood pressure. AZ: Arizona. OK: Oklahoma. ND: North Dakota. SD: South Dakota. Education was measured at Visit 1 of the SHS and is missing 109 participants with this information. Household income information is missing for 493 participants.

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Table 2. Participant Characteristics by Incident CVD and CVD Mortality Status (N = 1,818)[a]

		CVD Incident Event		CVD Death	
	Variable	No (n = 1, 240)	Yes (n = 578)	No (n = 1, 408)	Yes (n = 410)
Sex	Female	770 (62.1)	340 (58.8)	872 (61.9)	238 (58.0)
Center	AZ	137 (11.1)	49 (8.5)	162 (11.5)	24 (5.9)
	OK	563 (45.4)	224 (38.7)	612 (43.5)	175 (42.7)
	ND/SD	540 (43.5)	305 (52.8)	634 (45.0)	211 (51.4)
Smoking Status	Never	443 (35.7)	179 (31.0)	492 (35.0)	130 (31.7)
	Former	433 (34.9)	198 (34.2)	479 (34.0)	152 (37.1)
	Current	364 (29.4)	201 (34.8)	437 (31.0)	128 (31.2)
Diabetes	Yes	529 (42.7)	292 (50.5)	583 (41.4)	238 (58.0)
HT Treatment	Yes	450 (36.2)	207 (35.8)	465 (33.1)	192 (46.3)
Age (years)	Mean (SD)	63.8 (8.0)	64.1 (7.7)	63.2 (7.7)	66.2 (8.1)
BMI (kg/m^2)	Mean (SD)	30.5 (6.0)	31.0 (6.4)	30.7 (6.3)	30.3 (5.9)
SBP	Mean (SD)	131 (19.2)	132 (18.9)	130 (18.5)	134 (20.7)
LDL-chol	Mean (SD)	118 (32.8)	123 (30.9)	120 (32.5)	120 (31.7)
HDL-chol	Mean (SD)	43.2 (14.0)	42.0 (13.1)	43.0 (13.5)	42.1 (14.4)
eGFR (mL/min/1.73 m^2)	Mean (SD)	92.1 (22.2)	92.6 (21.1)	93.8 (20.6)	87.1 (25.0)
Blood lead (μg/L)	Mean (SD)	27.6 (18.5)	28.0 (28.2)	27.6 (22.2)	28.4 (21.6)
Blood cadmium (μg/L)	Mean (SD)	0.79 (0.68)	0.79 (0.59)	0.79 (0.67)	0.80 (0.61)

[a]BMI: body mass index. HT: hypertension. LDL: low-density lipoprotein. HDL: high-density lipoprotein. chol: cholesterol. eGFR: estimated glomerular filtration rate. SBP: systolic blood pressure. AZ: Arizona. OK: Oklahoma. ND: North Dakota. SD: South Dakota.

Table 3. Hazard Ratios (95% Confidence Interval) for Any Cardiovascular Disease and Coronary Heart Disease Incidence by Blood Lead (Modeled in the Original and Log Scale), with Policy Relevant Grouping for Lead Concentrations (N = 1,818)[d,f]

	≤10.0 μg/L (n = 132)	>10.0–35.0 μg/L (n = 1,261)	>35.0 μg/L (n = 425)	Per p80-p20 change (37.2–14.2 μg/L)[e]	Per p80-p20 change (13.2–3.5 μg/L)[f]
CVD Mortality					
Cases/noncases	26/106	277/984	107/318	410/1,408	410/1,408
Person years	2,088	19,309	5,220	26,617	26,617
Model 1[a]	1.00 (Reference)	0.84 (0.56, 1.28)	0.98 (0.61, 1.57)	1.05 (0.92, 1.19)	0.97 (0.80, 1.17)
Model 2[b]	1.00 (Reference)	1.01 (0.66, 1.54)	1.42 (0.98, 2.29)	1.17 (1.04, 1.31)	1.17 (0.96, 1.43)
Model 3[c]	1.00 (Reference)	0.99 (0.65, 1.51)	1.37 (0.84, 2.22)	1.15 (1.02, 1.30)	1.15 (0.93, 1.43)
CHD Mortality					
Cases/noncases	14/118	204/1,057	84/431	302/1,516	302/1,516
Person years	2,088	19,309	5,220	26,617	26,617
Model 1	1.00 (Reference)	1.15 (0.66, 2.00)	1.36 (0.74, 2.50)	1.08 (0.94, 1.24)	1.04 (0.83, 1.30)
Model 2	1.00 (Reference)	1.40 (0.80, 2.45)	2.08 (1.12, 3.85)	1.21 (1.08, 1.37)	1.30 (1.03, 1.64)
Model 3	1.00 (Reference)	1.40 (0.80, 2.46)	2.08 (1.11, 3.89)	1.22 (1.08, 1.37)	1.30 (1.02, 1.67)
Incident CVD					
Cases/noncases	41/91	413/848	124/301	578/1,240	578/1,240
Person years	1,918	16,982	4,655	23,555	23,555
Model 1	1.00 (Reference)	0.88 (0.63, 1.23)	0.78 (0.53, 1.15)	1.05 (0.95, 1.17)	0.95 (0.81, 1.11)
Model 2	1.00 (Reference)	0.98 (0.70, 1.37)	0.95 (0.64, 1.41)	1.11 (1.01, 1.23)	1.04 (0.88, 1.23)
Model 3	1.00 (Reference)	0.98 (0.70, 1.37)	0.95 (0.63, 1.42)	1.13 (1.02, 1.24)	1.05 (0.88, 1.25)
Incident CHD					
Cases/noncases	25/107	325/936	104/321	454/1,364	454/1,364
Person years	1,979	17,603	4,775	24,357	24,357
Model 1	1.00 (Reference)	1.04 (0.68, 1.58)	0.92 (0.57, 1.48)	1.01 (0.89, 1.14)	0.94 (0.78, 1.13)
Model 2	1.00 (Reference)	1.19 (0.78, 1.81)	1.21 (0.75, 1.96)	1.10 (0.98, 1.24)	1.09 (0.90, 1.31)
Model 3	1.00 (Reference)	1.20 (0.79, 1.84)	1.24 (0.76, 2.03)	1.12 (0.99, 1.25)	1.11 (0.91, 1.37)

[a]Model 1: Adjusted for sex, smoking status (never, former, current), BMI (kg/m^2), and eGFR (mL/min/1.73 m^2). [b]Model 2: Further adjusted for LDL-cholesterol (mg/dL) HDL-cholesterol (mg/dL), diabetes status (yes/no), systolic blood pressure (mmHg), and hypertension treatment (yes/no). [c]Model 3: Further adjusted for blood cadmium (modeled in the original scale). [d]All models included center of recruitment as a strata term, and age was accounted for in the follow-up times of all models. [e]Hazard ratios correspond to an increase in lead (modeled in the original scale) corresponding to the change across the 80th to 20th quantiles. [f]Hazard ratios correspond to an increase in lead (modeled in the log scale) corresponding to the change across the 80th to 20th quantiles. Cadmium was modeled in the log scale for this model only.

(31.8%) participants had incident CVD. Baseline blood lead concentrations were largely similar across participants with and without an incident CVD event before adjustment (Table 2). Participant characteristics were similar across CHD mortality and incident CHD status (Table S2).

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Modeling blood lead in policy-relevant groups of blood lead, the fully adjusted HR (95% CI) comparing the highest to the lowest group (>35.0 vs ≤10.0 μg/L) was 1.37 (0.84, 2.22) and 2.08 (1.11, 3.89) for CVD and CHD mortality, respectively, and 0.95 (0.63, 1.42) and 1.24 (0.76, 2.03) for incident CVD and incident CHD, respectively (Table 3). The corresponding associations using tertiles were not statistically significant (Table S3, Table S4). The adjusted HR (95% CI) for an 80th to 20th quantile change increase (37.2 vs 14.2 μg/L) in blood lead (modeled in the original scale) was 1.15 (1.02, 1.30) and 1.22 (1.08, 1.37) for CVD and CHD mortality, respectively, and 1.13 (1.02, 1.24) and 1.12 (0.99, 1.25) for incident CVD and incident CHD (Table 3). The corresponding adjusted HRs (95% CI) for blood lead modeled in the log scale were 1.15 (0.93, 1.43) and 1.30 (1.02, 1.67) for CVD and CHD mortality, respectively, and 1.05 (0.88, 1.25) and 1.11 (0.91, 1.37) for incident CVD and incident CHD (Table 3).

Sensitivity analyses adjusting for additional socioeconomic characteristics (educational attainment, household income), and removing eGFR, hypertension treatment at baseline, censoring at 90 years of age + follow-up time, removing outliers in blood lead, and removing systolic blood pressure produced similar results to the main models (Tables S5–S10).

Flexible dose–response models showed a general lack of association at lower blood lead concentrations and a linear positive increase with both CVD and CHD mortality and incidence after approximately 35 μg/L (Figure 1).

We observed no statistically significant effect modification between blood lead and CVD mortality or CVD incidence by age at baseline, sex, center, BMI, diabetes, and blood cadmium tertiles (Figure 2). Results were similar for CHD mortality and incidence (Figure S2).

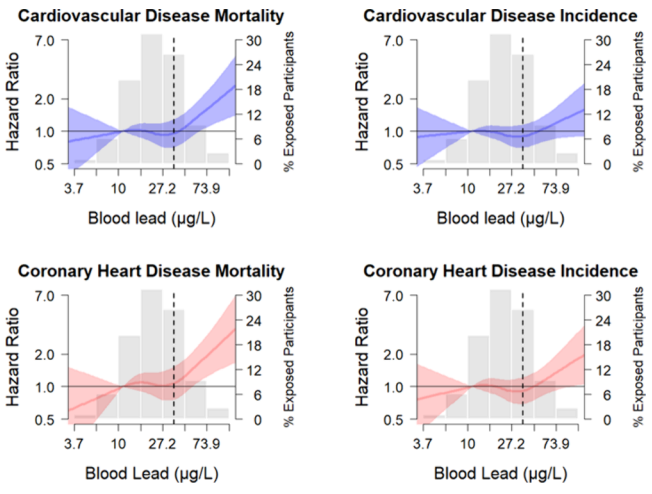

Figure 1. Associations between blood lead and cardiovascular disease mortality and incidence using restricted quadratic splines (N = 1,818). Hazard ratios incorporated restricted quadratic splines for log(lead) with knots at the 10th, 50th, and 90th percentiles, where the 10th percentile was treated as the reference. Solid lines represent adjusted hazard ratios, and shaded regions represent 95% confidence intervals. All models were adjusted for sex, smoking status (never, former, current), BMI (kg/m^2), estimated glomerular filtration rate (mL/min/1.73 m^2), LDL-cholesterol (mg/dL) HDL-cholesterol (mg/dL), diabetes status (yes/no), blood pressure (mmHg), and hypertension treatment (yes/no). Models included center of recruitment as a strata term, and age was accounted for in the follow-up times of all models. The vertical dashed line indicates 35 μg/L.

DISCUSSION

This study evaluated the impact of blood lead on CVD incidence and mortality in the SHS, a population across the U.S. Southwest and Great Plains with blood lead concentrations ranging from lower (<10 μg/L) to higher (>35 μg/L) levels. Among 410 CVD deaths and 578 CVD events occurring over 20 years of follow-up, increases in baseline blood lead were associated with higher mortality and incidence; the association with CHD mortality and incidence was similar. In flexible dose–response analyses, the associations appeared to be nonlinear; we observed a possible threshold with a clear increased risk of CVD and CHD mortality and incidence at blood lead concentrations above 35 μg/L. The findings were also largely consistent in the categorical models, except for incident CVD, although the hazard ratio comparing blood lead levels >35 to <10 μg/L was only statistically significant for CHD mortality. Findings between blood lead and composite CVD are likely driven by CHD, consistent with prior findings concerning lead and the development of atherosclerosis and related CHD outcomes.[47,48] We further report unadjusted associations between higher BMI and lower blood lead levels, consistent with findings from NHANES and numerous other populations.[44,49]

These findings add to the evidence for lead as a CVD risk factor[48] at lower to moderate blood lead levels, and call attention to promote actions to reduce exposure in communities with higher lead levels including American Indian and other communities in the U.S. and globally. Prior studies of lead and CVD risk were primarily performed using NHANES II (1976–80),[11] NHANES III (1988–1994),[12,14] NHANES 1999–2000[50] and NHANES 1999–2010/12.[13,16] There remains a need to replicate findings in different populations and prospective cohorts, including in American Indians, which are not well represented and sampled in federal health surveys.[51] The mean blood lead level in our study population was 27.8 μg/L. During sample collection (1998–1999), lead concentrations in the SHS (geometric mean: 23.0; 95% CI: 22.4–23.6 μg/L) were comparable to those observed in NHANES 1999–2000 (21.7; 95% CI: 20.8–22.6] μg/L), as previously reported.[32] Many studies of blood lead and CVD outcomes lack sufficient information at lower lead levels because laboratory measurements in previous decades were less sensitive than today. For instance, the detection limit was 10 μg/L (1.0 μg/dL) in NHANES III (1988–1994).[52] The current analysis had a lead detection limit in blood of 0.49 μg/L (0.049 μg/dL) and all participants had blood lead levels well above this level.

Findings on CVD risk are relevant given a recent SHS study showing that relatively small blood lead reductions (~1.0 μg/L) were related to an improvement in blood pressure levels.[53] These blood lead levels are common not only in American Indian and lower income communities in the U.S. but also in many low and middle-income countries, where lead exposure remains pervasive.[54,55]

Sustained public health efforts are needed to reduce environmental lead exposure both in American Indian communities and in other populations across the U.S. and globally. Lead contamination of drinking water has recently gained national attention in multiple settings across the U.S.[56,57] Ongoing state and federal efforts, including the Bipartisan Infrastructure Law and the Lead Pipe and Paint Action Plan[58–60] should contribute to removing this source of

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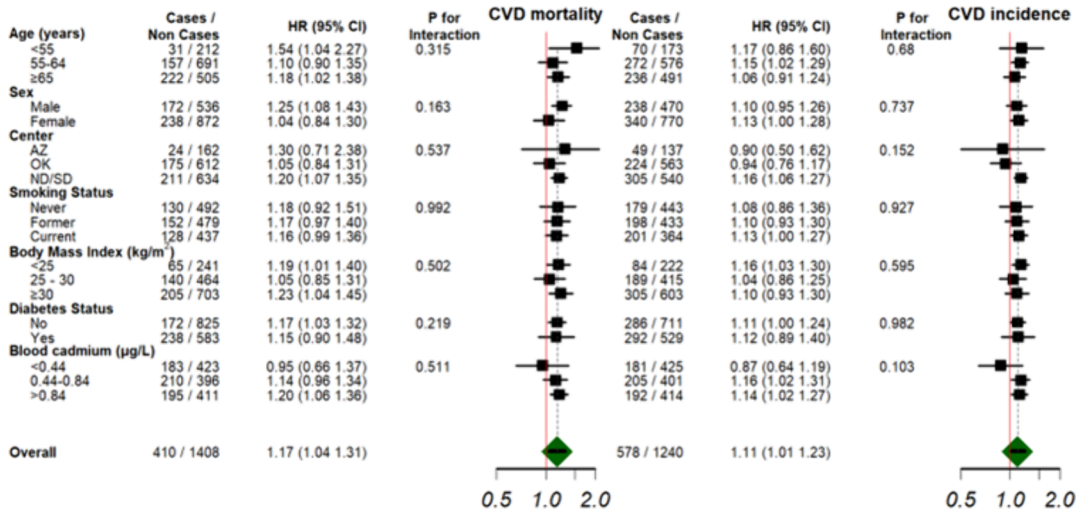

Figure 2. Hazard ratio (HR) (95% CI) of cardiovascular disease mortality (CVD) and CVD incidence by blood lead concentrations by participant subgroups. AZ indicates Arizona; OK, Oklahoma; and ND/SD, North Dakota/South Dakota. Hazard ratios correspond to the change across the 80th to 20th quantiles, and lead was modeled in the original scale. Models were adjusted for sex, smoking status (never, former, current), BMI (kg/m^2), estimated glomerular filtration rate (mL/min/1.73 m^2), LDL-cholesterol (mg/dL) HDL-cholesterol (mg/dL), diabetes status (yes/no), blood pressure (mmHg), and hypertension treatment (yes/no). Models included center of recruitment as a strata term, and age was accounted for in the follow-up times. Models included an interaction term between blood lead and the subgroup variable.

exposure. Airborne lead levels have also declined markedly in recent years in the U.S., specifically from 1.35 μg/m^3 in 1977 to 0.03 μg/m^3 in 2016.[61] However, soil pollution and lead-based paint in old housing remain major public health challenges in the U.S.[62] In the U.S. and other countries, important sources of exposure include food, cookware, cosmetics, toys, paints, spices, other consumer products and informal used lead-acid battery recyclers.[54,63] Collectively, American Indian communities experience an elevated burden of chronic metal exposures,[64,65] where a legacy of environmental contamination from mining remains a major concern.[66] Lead exposure also occurs from herbal supplements, spices, and tobacco products.[67−70] While there are ongoing efforts between tribal communities and the US-EPA to spread awareness and reduce lead exposure, especially among children,[71] our findings concerning CVD risk at lower lead levels complement the need for additional investment to reduce lead exposure.

No safe level of lead exposure has been identified.[27] Indeed, epidemiological data suggest that the health effects of lead are supra-linear,[72] meaning that the estimated adverse health effects associated with a given increase in blood lead are greater at lower levels than at higher levels. The supra-linear effect of lead on intelligence quotient (IQ) is well-established[73] and suggested for CVD mortality,[26] but we did not observe a supra-linear effect at lower blood lead levels. For CVD outcomes, the evidence is insufficient and limited at the low end of blood lead levels. Our finding of a potential threshold at blood lead levels below 35 μg/L needs to be confirmed in other populations.

Several chelating agents are effective at increasing lead excretion and removing it from the internal body storage.[74,75] Chelation is recommended at blood lead levels above 450 μg/L for children and above 700 μg/L for adults.[30] In the Trial to Assess Chelation Therapy 2 (TACT2), a trial that recruited participants with a prior MI and diabetes in 2016−2020, baseline median blood lead dropped from 9 to 3.5 μg/L at last infusion with disodium edetate vs no change with placebo infusion; the HR (95% CI) of cardiovascular outcomes for repeated chelation with disodium edetate vs placebo was 0.93 (0.76, 1.16), which was consistent with no efficacy.[76] Exposure prevention and reduction remain key public health actions to reduce CVD and other harmful effects associated with lead exposure.

This study is not without limitations. Roughly 9% of blood samples were clotted or lacked sufficient volume for metal analysis, reducing the sample size. However, the excluded blood samples had similar demographic characteristics (73% female vs 61% female), CVD event status (28% vs 32%), and CVD mortality (20% vs 23%) compared with the included samples, suggesting these excluded samples were not distinctly different from those analyzed. Smoking status was self-reported in the SHS, and it is possible that misclassification of smoking status could result in residual confounding. As other studies of lead and CVD have reported, other factors such as calcium deficiency that influence the distribution of lead in the body[6] could not be captured with our available data. To maximize power, this analysis also did not exclude those with CVD at recruitment, and this is similar to prior studies of metal and CVD using NHANES data.[15,77] Lastly, the collection supplies used during 1998−1999 were not prescreened for potential lead contamination. Our study has several strengths, including the large number of participants with blood lead measures, the high-quality outcome assessment performed in SHS, and the completeness of information concerning relevant confounders. This study not only includes a comprehensive list of relevant confounders in the main and in sensitivity analyses but also the distribution of potential confounders in the SHS is likely different than in NHANES and the U.S. general population, providing an important study population to add additional evidence on blood lead and CVD risk.

CONCLUSION

In this cohort study of American Indian adults, blood lead levels measured between 1998 and 1999, including those above the CDC, CSTE, and CDPH blood lead reference value of 35 μg/L, were associated with CVD and CHD mortality and

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incidence with a monotonic dose−response, with an increased risk at higher blood lead levels. Additional research is needed to confirm the shape of the dose−response, in particular, at levels below 35 μg/L, and whether there is a potential threshold in the low range of lead levels. Associations between blood lead and CVD mortality are similar to associations between blood lead and CHD mortality, suggesting that CHD drives this result, consistent with previous research from NHANES. Overall, these findings support evidence of lead as a CVD risk factor and highlight the importance of public health measures to reduce lead in communities across the U.S., including American Indian communities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/ehp.6c00057.

Tables of quality control results, participant characteristics, hazard ratios; figure of distribution of blood lead concentrations; text defining CHD (DOCX)

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Notes

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Indian Health Service, or the participating Tribal Nations. The data were collected, analyzed, and reported under agreements made with the sovereign tribal nations that have partnered in this research, which precludes commonly accepted modes of data sharing. Requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Strong Heart Study Coordinating Center at https://strongheartstudy.org/. Requests will be reviewed by tribal research partners before data may be released. This policy is consistent with the "NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data." Strong Heart Study data are owned by the participating tribes and are not available for public use.
The authors declare no competing financial interest.

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that they have no actual or potential competing financial interests.

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