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Do we underestimate risk of cardiovascular mortality due to lead exposure?

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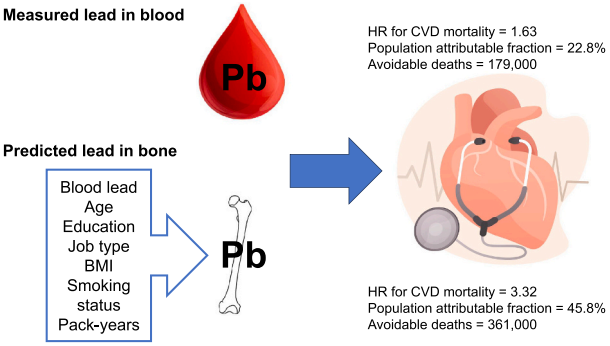
HIGHLIGHTS

- We examined the associations of algorithm-estimated bone lead and mortality using NHANES-III data.
- The associations for cardiovascular mortality were greater with bone lead compared to blood lead.
- The estimated number of cardiovascular deaths attributable to bone lead in the US was approximately 360,000 annually.
- Cardiovascular mortality risk associated with blood lead may have underestimated the true effects.
- Utilizing bone lead as exposure markers could yield a more accurate estimation of the mortality risk.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Studies using data from the National Health and Nutrition Examination Survey-III (NHANES-III) have demonstrated significant prospective associations between blood lead levels and increased mortality. Bone lead represents cumulative lead burden and thus is a better biomarker for assessing chronic impacts, but its in vivo assessment requires special K-x-ray fluorescence (KXRF) instrumentation. Our team recently developed an algorithm predicting bone lead levels from a combination of blood lead levels, age and other socioeconomic and behavioral variables. We examined the associations of our algorithm-estimated bone lead levels and mortality in NHANES-III.

Methods: We included 11,628 adults followed up to December 31, 2019. Estimated tibia lead and patella lead levels were calculated using our prediction algorithms. We used survey-weighted Cox proportional hazards models to compute hazard ratios (HRs) and 95 % confidence intervals (CIs).

Results: During the median follow-up of 26.8 years, 4900 participants died (mortality rate = 1398 per 100,000 adults/year). Geometric means (95 % CIs) of blood lead, predicted tibia lead, and predicted patella lead were 2.69 μg/dL (2.54, 2.84), 6.73 μg/g (6.22, 7.25), and 16.3 μg/g (15.9, 16.8), respectively. The associations for all-cause mortality were similar between blood lead and bone lead. However, the associations for cardiovascular mortality were much greater with predicted bone lead markers compared to blood lead: for comparing participants at the 90th vs. 10th percentiles of exposure, HR = 3.32 (95 % CI: 1.93–5.73) for tibia lead, 2.42 (1.56–3.76) for patella lead, 1.63 (1.25–2.14) for blood lead. The population attributable fractions for

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cardiovascular disease mortality if everyone's lead concentrations were declined to the 10th percentiles were 45.8 % (95 % CI: 28.1–59.4) for tibia lead, 33.1 % (18.1–45.8) for patella lead, and 22.8 % (10.4–33.8) for blood lead.

Conclusions: These findings suggest that risk assessment for cardiovascular mortality based on blood lead levels may underestimate the true mortality risk of lead exposure.

1. Introduction

Lead exposure at non-occupational, community-levels of exposure has been identified as a risk factor for hypertension, cardiovascular disease (CVD), and cardiovascular mortality in a growing body of research. Several potential mechanisms for these impacts have been demonstrated in experimental studies, such as the lead's ability to increase blood pressure through increases in angiotensin II levels, increases in Na+/K + -ATPAase activity, reductions in nitric oxide bioavailability, and increases in the activity of matrix metalloproteinases (Nascimento et al., 2015; Vaziri, 2008). Lead has also been shown to induce the proliferation of vascular smooth muscle cell and promote oxidative stress and atherosclerosis in animal models (Fujiwara et al., 1995; Tarugi et al., 1982).

The epidemiological research supporting lead's cardiovascular effects at population levels of exposure has included cross-sectional, case-control, retrospective and prospective cohort, and human experimental studies spanning multiple countries. A recent American Heart Association scientific statement concluded that lead is a significant risk factor for CVD, including ischemic heart disease, stroke, and peripheral artery disease (Lamas et al., 2023). In addition, studies have continued to accumulate, including a number of prospective studies demonstrating a significant association between lead exposure in samples of the general population and cardiovascular mortality(Aoki et al., 2016; Khalil et al., 2009; Lanphear et al., 2018; Menke et al., 2006; Schober et al., 2006; Weisskopf et al., 2009).

A nuance that is critical to understanding the public health ramifications of this research is that almost all of these prospective studies used blood lead levels (BLLs) at a single point in time to indicate the participants' exposure to lead. BLLs represent circulating lead from both the absorption of external lead exposure (primarily through inhalation and/or ingestion) as well as lead mobilized from internal organs. Although the half-life of BLLs of 25–35 days is widely quoted in the literature, these values primarily represent the rate of BLL decline if the exposure period is short (e.g., < 30 days) (Rentschler et al., 2012). In contrast, upon the cessation of long-term lead exposure (spanning years to decades), as is more typical in adults who had experienced population-wide exposures to, for example, atmospheric lead from the combustion of leaded gasoline or drinking water from lead contaminated plumbing, the clearance of lead from the blood is much slower, reflecting the equilibrium that exists between blood and other soft-tissue pools of lead with lead from the long-lived deposits in bone. Bone stores of lead typically represent the storage site of 90–95 % of an individual's lead burden and have a half-life of decades (Hu et al., 2007).

Thus, it is elusive to determine the extent to which a BLL in an adult at a single point of time represents on-going acute lead exposure or lead mobilization from long-term bone storage sites. In the context of epidemiological studies demonstrating that a single measurement of blood lead predicts subsequent increased cardiovascular mortality, distinguishing between these scenarios has profound implications for risk assessment and public health. For example, would a population with elevations in blood lead from new industrial activity be immediately at risk for adverse long-term cardiovascular outcomes, or would such risks only develop after years to decades of exposure?

There has been a growing body of epidemiological research using K-x-ray fluorescence (KXRF) as a non-invasive technique to measure lead in bone. Among several studies applying this method, cross-sectional and prospective studies were conducted involving community-exposed men participating in the Normative Aging Study in Boston. These studies demonstrated that the measured bone lead levels were stronger than BLLs, both cross-sectionally and prospectively, in associations with the development of hypertension (Cheng et al., 2001; Hu et al., 1996a), ischemic heart disease (Jain et al., 2007), and cardiovascular mortality (Weisskopf et al., 2009).

Measurements of bone lead using KXRF requires specialized equipment and significant time with each participant, however, obviating its application to very large population studies. In view of this limitation, our study team used the data from the Normative Aging Study to develop algorithms predicting bone lead levels from BLLs and standard biochemical, hematologic, and questionnaire data that are typically available in large population studies (Park et al., 2009). Recently, we developed a new algorithm using an ensemble machine learning approach, Super Learner, which provided better prediction performance for bone lead concentrations (Wang et al., 2022). We then applied these algorithms to data from the Third National Health and Nutrition Examination Survey (NHANES III) and found that the estimated bone lead values were significantly associated with high blood pressure with relationships that were stronger than that of BLLs (Park et al., 2009; Wang et al., 2022).

Considering the recent study by Lanphear et al. that utilized data from NHANES III and the National Death Index to demonstrate that BLLs significantly predicted increased mortality from all-causes, CVD, and ischemic heart disease, with overall impacts on mortality substantially greater than previous estimates (Lanphear et al., 2018), we carried out a similar analysis of NHANES III data with the addition of bone lead levels estimated using the new machine-learning algorithm as an exposure variable.

2. Methods

2.1. Study population and data

We used data from NHANES-III linked to the National Death Index (NDI) mortality data. NHANES is administered by the National Center for Health Statistics and approved by their Institutional Review Board. All participants of NHANES were required to provide written informed consent. For the present study, we tried to replicate the study by Lanphear et al. and included the same covariates considered by Lanphear et al. (Lanphear et al., 2018). The NHANES-III Adults data included a total of 20,050 adults aged ≥18 years. We excluded participants whose age <20 years and who had missing data in blood lead or mortality (n = 3779). We also excluded participants whose bone lead predicted values were missing due to missing information on bone lead predictors (education, white collar occupation, smoking status, pack-years of cigarette, and body mass index) (n = 1953). We additionally excluded those who were missing in core covariates (i.e., income, urinary cadmium, alcohol consumption, hemoglobin A1c, cotinine, and healthy eating index score) (n = 2223). Finally, we excluded those who had 0 month of follow-up (n = 2); and other race/ethnicity (n = 465), which yielded the final sample size of 11,628 (Suppl Fig. S1).

To make our analysis comparable to that of the study of Lanphear et al.(Lanphear et al., 2018), we considered the same covariates used in their regression models: age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American), household income (<US $20,000 or ≥ $20,000 per year), body mass index (BMI: normal [<25.0 kg/m^2], overweight [25.0–29.9 kg/m^2], or obese [≥30.0 kg/m^2]),

smoking status (never, former, or current), hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), urinary cadmium (tertiles [μg/g]), alcohol consumption (four or fewer or more than four drinks per month), physical activity in previous month (none, one to 14 times, 15 or more times), healthy eating index (tertiles), serum cholesterol, and hemoglobin A1c. For bone lead prediction, the following additional variables were included: education (<high school, high school graduate and some college, ≥4 years of college), job type (white collar, or other), and pack-years of cigarette. NHANES imputed BLLs below the limit of detection (LOD, 1 μg/dL, 8.3 %) with LOD/$\sqrt{2}$ (0.7 μg/dL).

We used the public-use mortality file that is linked to NHANES-III. (CDC/National Center for Health Statistics, 2022) The available mortality follow-up data has been updated through December 31, 2019, which is 8 more years of follow-up times than the study by Lanphear et al. (through December 31, 2011). Cause-of-death coding follows either the 9th revision of the International Statistical Classification of Diseases (ICD-9, deaths before 1999) or the 10th revision (ICD-10, death after 1998). The public-use linked mortality file provides ICD-10 based underlying cause-of-death groups with a recode of all ICD-9 based mortality data. For the present study, we included mortality from all causes, heart disease (ICD-10 I00-I09, I11, I13, I20-I51), and CVD (heart disease and cerebrovascular disease: ICD-10 I00-I09, I11, I13, I20-I51, I60-I69).

2.2. Bone lead prediction

Each participant included in the analysis was assigned predicted concentrations for patella and tibia lead. These predictions were calculated using an ensemble of eight different algorithms (linear regression, generalized additive model, ridge regression, least absolute shrinkage and selection operator, elastic-net, classification and regression tree, random forest, and XGBoost) based on the following 7 predictors: blood lead concentration (continuous, log-transformed), age (continuous, years), education (categorical: <high school, high school graduate and some college, ≥4 years of college), job type (binary: white collar, other), body mass index (continuous, kg/m^2), smoking status (categorical: never, former, current), and cumulative cigarette smoking (continuous, pack-years) (Wang et al., 2022). The most important predictors for patella lead were blood lead concentration and age, in that order. Conversely, the most significant predictors for tibia lead were age followed by blood lead concentration. The predictive performances based on Pearson correlation coefficients between observed and predicted values were 0.52 for tibia (cortical bone) and 0.58 for patella lead (trabecular bone). If the observed concentrations fall below 20 μg/g for tibia lead and 30 μg/g for patella lead (mean concentrations in the Normative Aging Study), the models have a tendency to overestimate the observed values. On the other hand, they are likely to underestimate the observed values when faced with higher concentrations. The prediction models are available at https://github.com/XinWangUmich/Bone-Lead-Prediction-Models.

2.3. Statistical analysis

All analyses were conducted in R (version 4.2.0, R Foundation for Statistical Computing) and SAS (version 9.4). Statistical significance was defined at $\alpha < 0.05$. The survey components including cluster, strata and sampling weights were used to account for the complex sampling design. We used survey-weighted Cox proportional hazards models to evaluate the associations between each lead variable and mortality outcomes (svycoxph from the package survey in R). All regression models were adjusted for the same covariates used in Lanphear et al. (2018) except age because age was used as the time scale: sex, race/ethnicity, household income, BMI, smoking status, hypertension, urinary cadmium, alcohol consumption, physical activity, healthy eating index, serum cholesterol, and hemoglobin A1c. We used attained age, the sum of baseline age and follow-up time, as the time scale to account for the potential misspecification of the hazard function that could happen when time-on-study is used as the time scale (Korn et al., 1997; Park et al., 2020). Blood lead and bone lead variables were log-transformed because the dose-response shape was close to log-linear, and thus log-transformation improved linearity of the associations. Because the predicted tibia lead variable had some negative values (10.4 %, due to the imprecision associated with the estimations when the true values are likely close to 0), we added a constant (9.607 which is the absolute value of the minimum (−8.607) plus 1) before log-transformation. Hazard ratios (HRs) and 95 % confidence intervals (CIs) were computed comparing the 90th vs. the 10th percentile at the log-scale of each exposure variable to be consistent with Lanphear et al. (2018). We also computed HRs and 95 % CIs comparing the lowest vs. higher tertiles to better capture non-linear dose-response relationships. Linear trends were tested by fitting the tertile variable as ordinal in the models. We used the scaled Schoenfeld residuals and confirmed that the proportional hazards assumption held for all covariates.

We evaluated if the associations differ by sex and race/ethnicity using stratified analyses. Only linear lead variables were used in this analysis due to the power issue.

We computed population attributable fractions (PAF) using the approach used in the disease burden for continuous risk factors (Vander Hoorn et al., 2004). PAF in this study indicates the proportional reduction in each mortality that would occur if each exposure concentration in the population were reduced to the counterfactual of theoretical-minimum-risk exposure distribution. To be consistent with Lanphear et al. (2018), we used the 10th percentiles of each lead concentration as the theoretical-minimum-risk exposure distributions. Relative risks used to compute PAFs were based on adjusted HRs comparing the 90th vs. the 10th percentile of each continuous lead variable. The numbers of avoidable (excess) deaths for each lead that would have been prevented annually in the US were based on the average annual number of deaths from all causes (2,495,686), CVD (787,183), and heart disease (643,488) from 1999 to 2019 (CDC, 2023, 2020).

To make proper comparisons between the Lanphere study and the present study, we conducted sensitivity analyses. First, we restricted the follow-up time until December 31, 2011. Next, we employed time-on-study (follow-up time) instead of attained age as the time scale. It should be noted that we used “heart disease” based on ICD-10 I00-I09, I11, I13, I20-I51, whereas the Lanphere study examined “ischemic heart disease” which was based on ICD-9410–414; ICD-10 I20–I25). Ischemic heart disease mortality was not available in the public-use mortality file.

Finally, we evaluated the added value of the predicted bone lead variable to the model with the predictors of bone lead markers. One may argue that the predicted bone lead variables could be associated with CVD mortality because the predictors of bone lead markers are also known to be independent predictors of CVD mortality, and thus the predicted bone lead variables may just act as proxies for those other known CVD mortality predictors. To address this, we first fit a model with the predictors of bone lead markers (age, BMI, education, job type, smoking status and pack-years) with time-on-study as the time scale. Then each lead marker was added to the model and HRs (95 % CIs) were computed comparing the 90th vs. the 10th percentile at the log-scale of each lead variable.

3. Results

A total of 11,628 participants were included in the analysis which represented 136 millions of the general US population aged 20 and older. The sample-weighted mean age was 44.3 years (95 % CI, 43.3, 45.3) and 51.9 % were females (Table 1). The geometric means (95 % CIs) of blood lead, predicted tibia lead, and predicted patella lead were 2.69 μg/dL (2.54, 2.84), 6.73 μg/g (6.22, 7.25), and 16.3 μg/g (15.9, 16.8), respectively. All covariates except urban residence were

Table 1
Characteristics of the study population for all and by tertiles of blood lead concentrations (n = 11,628).

	All	Blood lead tertiles			
		Tertile 1 (≤ 2.2 μg/dL)	Tertile 2 (2.3–4.2 μg/dL)	Tertile 3 (≥4.3 μg/dL)	
Continuous variables	Mean or GM (95 % CI)				*P*-value
Blood lead, μg/dL*	2.69 (2.54, 2.84)	1.31 (1.28, 1.35)	3.11 (3.09, 3.14)	6.44 (6.29, 6.60)	<0.0001
Predicted tibia lead, μg/g*	6.73 (6.22, 7.25)	2.48 (2.08, 2.91)	8.18 (7.65, 8.73)	13.3 (12.6, 14.0)	<0.0001
Predicted patella lead, μg/g*	16.3 (15.9, 16.8)	12.3 (11.9, 12.6)	16.3 (15.8, 16.8)	25.1 (24.5, 25.7)	<0.0001
Age, years	44.3 (43.3, 45.3)	38.7 (37.8, 39.7)	46.0 (44.8, 47.1)	50.5 (49.0, 52.0)	<0.0001
Total cholesterol, mg/dL	205 (203, 206)	197 (195, 199)	207 (204, 210)	212 (210, 214)	<0.0001
HbA1c, %	5.34 (5.29, 5.40)	5.21 (5.15, 5.28)	5.40 (5.34, 5.46)	5.47 (5.40, 5.54)	<0.0001
Serum cotinine, ng/mL*	1.75 (1.45, 2.11)	0.68 (0.56, 0.82)	2.12 (1.70, 2.63)	5.58 (4.27, 7.30)	<0.0001
Urinary cadmium, μg/g creatinine*	0.33 (0.31, 0.36)	0.24 (0.22, 0.27)	0.34 (0.31, 0.37)	0.53 (0.49, 0.56)	<0.0001
Healthy eating index score	63.7 (63.0, 64.3)	64.5 (63.6, 65.4)	64.0 (63.4, 64.7)	61.9 (61.1, 62.8)	<0.0001
Categorical variables	Unweighted N (weighted %)				P-value
Female	6125 (51.9)	3004 (72.2)	1968 (44.9)	1153 (30.5)	0.0002
Race/Ethnicity					<0.0001
Non-Hispanic White	5306 (84.4)	1848 (85.8)	1881 (85.4)	1577 (81.2)	
Non-Hispanic Black	3225 (10.6)	1048 (9.46)	1028 (9.82)	1149 (13.2)	
Mexican American	3097 (5.00)	1059 (4.76)	1023 (4.74)	1015 (5.59)	
High-school education or higher	7226 (77.9)	2907 (85.9)	2471 (77.3)	1848 (66.7)	<0.0001
Income>US$20,000	6308 (70.0)	2411 (73.7)	2164 (71.6)	1733 (62.3)	<0.0001
Urban residence	5559 (45.7)	1773 (44.3)	1849 (44.6)	1937 (49.4)	0.3759
Smoking status					<0.0001
Never	5859 (46.2)	2615 (60.0)	1928 (44.2)	1316 (28.2)	
Former	2921 (26.3)	762 (22.3)	1054 (26.6)	1105 (31.8)	
Current	2848 (27.5)	578 (17.7)	950 (29.2)	1320 (40.0)	
Alcohol intake (drinks per month)					<0.0001
Four or fewer	7428 (56.6)	2913 (64.5)	2511 (54.9)	2004 (47.1)	
More than four	4200 (43.4)	1042 (35.5)	1421 (45.1)	1737 (52.9)	
Physical activity (per month)					<0.0001
None	3364 (19.6)	1091 (18.8)	1093 (18.7)	1180 (21.8)	
One to 14 times	4502 (41.4)	1551 (41.8)	1523 (41.4)	1428 (40.6)	
15 or more times	3762 (39.1)	1313 (39.4)	1316 (39.9)	1133 (37.5)	
Hypertension	2600 (16.5)	586 (11.0)	923 (18.1)	1091 (22.8)	<0.0001
Body mass index					<0.0001
Normal weight (<25 kg/m^2)	4528 (44.1)	1609 (46.8)	1422 (42.0)	1497 (42.8)	
Overweight (25–29.9 kg/m^2)	4128 (33.6)	1256 (28.9)	1440 (36.1)	1432 (37.3)	
Obese (≥30 kg/m^2)	2972 (22.3)	1090 (24.3)	1070 (21.9)	812 (19.9)	
Mortality					
Follow-up years, median (Q1, Q3)	26.8 (22.1, 28.7)	27.2 (25.7, 28.7)	26.7 (20.7, 28.7)	25.8 (14.1, 28.5)	–
Number of deaths, unweighted N (weighted %)					
All-causes	4900 (33.4)	1025 (19.5)	1708 (35.6)	2167 (51.3)	<0.0001
CVD	1791 (11.1)	349 (5.58)	633 (12.2)	809 (17.9)	<0.0001
Heart disease	1471 (9.3)	264 (4.26)	524 (10.3)	683 (15.3)	<0.0001
Mortality rate, 100,000 person-years					
All-causes	1398	758	1499	2410	–
CVD	464	217	511	841	–
Heart disease	388	166	435	720	–

Cardiovascular disease (CVD): ICD-10 I00-I09, I11, I13, I20-I51, I60-I69.
Heart diseases: ICD-10 I00-I09, I11, I13, I20-I51.
* Median (Q1, Q3).

associated with teriles of blood lead concentrations. Participants in the top tertile of blood lead were older, less likely to be female, less likely to be non-Hispanic White, less educated, more likely to be former or current smokers, to drink more, and less physically active. BLLs were moderately correlated with both predicted tibia lead levels (correlation coefficient between log-transformed blood lead and log-transformed predicted tibia lead = 0.57) and predicted patella lead levels (correlation coefficient between log-transformed blood lead and log-transformed predicted patella lead =0.59). During the median follow-up of 26.8 years, 4900 participants died (mortality rate = 1398 per 100,000 person-years). Among them, 1791 died from CVD (mortality rate = 464 per 100,000 person-years), and 1471 died from heart disease (mortality rate = 388 per 100,000 person-years) (Table 1).

Table 2 shows the survey-weighted Cox regression results. The associations for all-cause mortality were similar between blood lead and bone lead. However, the associations for CVD and heart disease mortality were much greater with bone lead markers compared to blood lead: for CVD mortality comparing participants at the 90th vs. 10th percentiles of exposure, HR = 3.32 (95 % CI: 1.93–5.73) for predicted tibia lead, 2.42 (1.56–3.76) for predicted patella lead, 1.63 (1.25–2.14) for blood lead; for heart disease mortality, 3.35 (1.91–5.88) for predicted tibia lead, 2.39 (1.52–3.76) for predicted patella lead, and 1.76 (1.36–2.28) for blood lead. The significant dose-dependent associations for CVD and heart disease mortality were confirmed when tertiles of lead variables were fit.

In sensitivity analyses, we confirmed similar HRs when using the same follow-up period (until December 31, 2011) and time-on-study as the time scale (Suppl Table S1). As expected, there was a relatively larger difference in HRs for the association between blood lead and heart disease mortality (HR = 2.08 (95 % CI: 1.52, 2.85) for the Lanphere study vs. HR = 1.96 (95 % CI: 1.37, 2.80) for the present study). When the follow-up was restricted to December 31, 2011, similar HRs were observed when age was the time scale for blood lead, whereas smaller HRs for all-cause and similar HRs for CVD and heart disease mortality were observed when age was used as the time scale, compared with time-on-study. When the follow-up was extended to December 31, 2019, all HRs were attenuated. We noted consistently larger HRs for predicted bone lead variables compared to those for blood lead when other

Table 2
Hazard ratios (95 % confidence intervals) of mortality from all-causes, cardiovascular disease (CVD), and heart disease comparing the 90th vs the 10th percentiles and by tertiles of lead biomarkers in the NHANES-III (n = 11,628).

	Tertile 1	Tertile 2	Tertile 3	P for trend	Continuous (90th vs. 10th)*
All-causes					
Blood lead	Ref	1.05 (0.95, 1.17)	1.20 (1.06, 1.35)	0.002	1.21 (1.04, 1.40)
Predicted tibia lead	Ref	1.29 (1.03, 1.60)	1.23 (0.99, 1.53)	0.33	1.16 (0.89, 1.52)
Predicted patella lead	Ref	1.31 (1.06, 1.62)	1.31 (1.05, 1.64)	0.07	1.24 (1.01, 1.51)
CVD					
Blood lead	Ref	1.24 (1.02, 1.52)	1.52 (1.19, 1.94)	0.001	1.63 (1.25, 2.14)
Predicted tibia lead	Ref	2.39 (1.49, 3.84)	3.09 (1.93, 4.95)	<0.0001	3.32 (1.93, 5.73)
Predicted patella lead	Ref	2.36 (1.41, 3.97)	2.68 (1.54, 4.64)	0.005	2.42 (1.56, 3.76)
Heart					
Blood lead	Ref	1.36 (1.11, 1.67)	1.62 (1.28, 2.05)	0.0001	1.76 (1.36, 2.28)
Predicted tibia lead	Ref	2.84 (1.68, 4.80)	3.60 (2.08, 6.24)	0.0002	3.35 (1.91, 5.88)
Predicted patella lead	Ref	2.45 (1.27, 4.71)	2.72 (1.38, 5.34)	0.02	2.39 (1.52, 3.76)

All models were adjusted for sex, ethnic origin (non-Hispanic White, non-Hispanic Black, or Mexican-American), household income (<US$20000 or ≥ $20,000 per year), body-mass index (normal [<25 kg/m^2], overweight [25–29.9 kg/m^2], or obese [≥30 kg/m^2]), smoking status (never, current, or former), hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), urinary cadmium (tertiles), alcohol consumption (four or fewer or more than four drinks per month), physical activity in previous month (none, one to 14 times, 15 or more times), healthy eating index (tertiles), serum cholesterol (continuous), and glycated hemoglobin (continuous). Age was used as the time scale in survey-weighted Cox proportional hazards models.

* Hazard ratios and 95 % CIs were computed as the risk for an increase from 10th to 90th percentiles at the log-scale of each exposure variable which was fit as continuous.

Table 3
Population attributable fractions (PAFs) and avoidable deaths for all-causes, cardiovascular disease (CVD), and heart disease in relation to blood lead and bone lead markers in the NHANES-III (n = 11,628).

	Blood lead	Predicted tibia lead	Predicted patella lead
All causes			
PAF	8.9 % (1.3, 16.0)	7.2 % (−5.9, 18.9)	9.0 % (0.5, 16.9)
Avoidable deaths	222,000 (32,000–399,000)	180,000 (NA*, 472,000)	225,000 (12,000, 422,000)
CVD			
PAF	22.8 % (10.4, 33.8)	45.8 % (28.1, 59.4)	33.1 % (18.1, 45.8)
Avoidable deaths	179,000 (82,000–266,000)	361,000 (221,000–468,000)	261,000 (142,000–361,000)
Heart			
PAF	26.0 % (14.7, 36.1)	46.0 % (27.8, 60.0)	32.7 % (17.1, 45.8)
Avoidable deaths	167,000 (95,000–232,000)	296,000 (179,000–386,000)	210,000 (110,000–295,000)

PAF was computed using the approach used in the disease burden for continuous risk factors(Vander Hoorn et al., 2004) and the 10th percentiles of each lead concentration as the theoretical-minimum-risk exposure distributions consistent with Lanphear et al.(Lanphear et al., 2018) The numbers of avoidable (excess) deaths for each lead that would have been prevented annually in the US were based on the average annual number of deaths from all causes (2,495,686), CVD (787,183), and heart disease (643,488) from 1999 to 2019.(Centers for Disease Control and Prevention (CDC), 2020, 2023).

* Avoidable death was not computed because the corresponding relative risk was negative.

conditions remained identical.

The PAFs for CVD mortality if each exposure concentration in the population were dropped to the 10th percentiles were 45.8 % (95 % CI: 28.1–59.4) for predicted tibia lead, 33.1 % (18.1–45.8) for predicted patella lead, and 22.8 % (10.4–33.8) for blood lead (Table 3). Given that 787,183 Americans died from CVD annually over the past 2 decades in the US, approximately 261,000 to 361,000 CVD mortality cases annually in the US were attributable to cumulative lead exposure (predicted bone lead), which are up to twice greater than the avoidable deaths due to blood lead (179,000 CVD mortality cases). Similar PAFs were found for heart disease mortality, whereas relatively modest PAFs (7.2 % to 9.0 %) were found for all-cause mortality.

The associations between predicted bone lead and mortality differed by race/ethnicity but the directions depended on different causes of mortality (Fig. 1 and Suppl Table S2). The associations between lead markers and all-cause mortality were greater in non-Hispanic Black participants (HR = 1.50 (1.20–1.87) for blood lead; 1.73 (1.18–2.53) for predicted tibia lead; 2.09 (1.60–2.74) for predicted patella lead) compared with non-Hispanic White and Mexican American participants. On the other hand, the associations between lead markers and CVD mortality were positive in non-Hispanic White and non-Hispanic Black participants whereas those were null in Mexican American participants. There were no differences in the associations by sex.

We compared the associations between lead markers and CVD mortality in the model with the predictors of bone lead markers (Table 4). Predicted bone lead markers had significant and greater HRs than blood lead (HR = 4.81 (95 % CI: 2.27–10.2) for predicted tibia lead, 3.03 (1.74–5.29) for predicted patella lead, 1.65 (1.32–2.05) for blood lead comparing participants at the 90th vs. 10th percentiles of exposure).

4. Discussion

Epidemiological studies on the association between environmental toxicants and human health rely on available exposure assessment data. Biomarkers are considered objective indicators of exposures of interest and therefore are widely used. In the case of lead exposure, blood lead is recognized as a valid biomarker and has been extensively used in previous studies of lead toxicity in the population. Although numerous previous studies have consistently reported a positive association between blood lead and cardiovascular mortality in the US general population, a crucial question remains unanswered: *Are we accurately estimating the cardiovascular toxicity of long-term lead exposure?* This study suggests that the cardiovascular mortality effects reported in previous

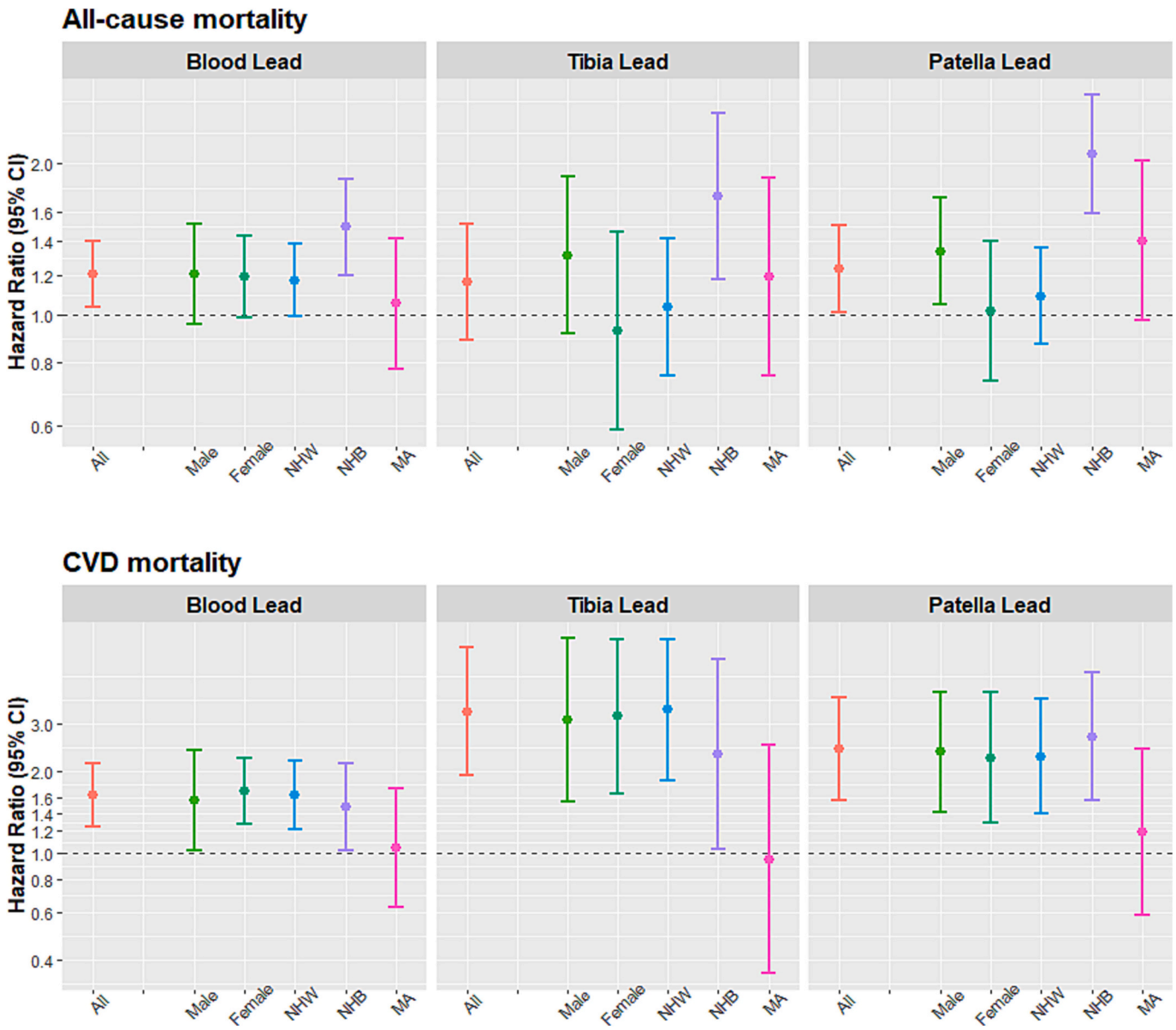

Fig. 1. Hazard ratios (95 % confidence intervals) of mortality from all-causes and cardiovascular disease (CVD) comparing the 90th vs the 10th percentiles of lead biomarkers by sex and race/ethnicity. See Table 2 for more details of modeling. NHW, non-Hispanic White; NHB, non-Hispanic Black; MA, Mexican American.

studies, based on BLLs, may have been underestimated.

The present study proposes that the use of predicted bone lead variables could better capture long-term cumulative lead exposure and thus provide a more precise estimation of the cardiovascular mortality risk associated with lead exposure in the US. The findings suggest that the true cardiovascular mortality effects of lead exposure in the US could be approximately 1.5 to 2 times greater than what has been previously. Specifically, the HRs for comparing participants in the 90th vs the 10th percentiles of predicted patella lead and predicted tibia lead were estimated to be 2.42 (95 % CI, 1.56–3.76) and 3.32 (1.93–5.73), respectively, compared to an HR of 1.63 (1.25–2.14) for blood lead. The estimated number of CVD deaths attributable to lead exposure in the US was approximately 180,000 annually if blood lead was used as an exposure marker, but this number would double to 360,000 deaths per year if predicted tibia lead was used instead. These results suggest that risk assessments based on BLLs may underestimate the actual mortality risk of lead exposure. We also confirm that predicted bone lead variables were associated with CVD mortality independent of the predictors of bone lead markers (age, BMI, education, job type, smoking status and pack-years).

We did not find any differences in the risk of all-cause mortality by different lead biomarkers. This suggests that the cardiovascular system might be particularly susceptible to the effects of cumulative lead exposure. Bone lead represents cumulative lead burden because the majority (90–95 %) of lead burden in adults is stored in the skeleton (Hu et al., 2007). With aging, especially when the bone turnover rate is rising, lead in the bone is released to the circulation system and thus serves as an endogenous source of exposure (Hu et al., 1996b). Major biological mechanisms involve vascular and endothelial function by promoting oxidative stress and inflammation, diminishing nitric oxide bioavailability, increasing vasoconstrictor prostaglandins and decreasing vasodilator prostaglandins, and interrupting vascular smooth muscle calcium signaling (Vaziri, 2008). Epidemiologic studies have supported the link between bone lead and cardiovascular health endpoints. In a prospective study of men in the greater Boston area, the Normative Aging Study, higher patella lead levels were associated with an increased risk of ischemic heart disease mortality (HR = 1.87 (95 % CI, 0.77–4.53) comparing the highest vs lowest tertiles) but the

Table 4
Evaluation of the added value of the predicted bone lead variable to the model with the predictors of bone lead markers. Hazard ratios and 95 % confidence intervals of cardiovascular disease mortality are presented (n = 11,628).

	Bone lead predictors only	Adding blood lead	Adding predicted tibia lead	Adding predicted patella lead
Age (for 10 yrs)	3.23 (3.05, 3.41)	3.16 (2.99, 3.34)	2.54 (2.23, 2.89)	2.69 (2.41, 3.00)
BMI (for IQR, 6.8 kg/m^2)	1.33 (1.22, 1.45)	1.34 (1.23, 1.47)	1.27 (1.16, 1.39)	1.30 (1.19, 1.42)
High school graduate and some college (vs. <high school)	0.89 (0.78, 1.01)	0.90 (0.79, 1.03)	0.99 (0.86, 1.15)	0.97 (0.84, 1.12)
≥4 years of college (vs. <high school)	0.71 (0.55, 0.92)	0.71 (0.55, 0.91)	0.92 (0.70, 1.21)	0.86 (0.66, 1.13)
White collar (vs. other)	0.90 (0.77, 1.06)	0.93 (0.80, 1.09)	1.00 (0.85, 1.16)	1.00 (0.86, 1.18)
Former smokers (vs. never)	1.20 (1.01, 1.41)	1.14 (0.97, 1.35)	1.08 (0.92, 1.26)	1.11 (0.94, 1.32)
Current smokers (vs. never)	2.07 (1.77, 2.42)	1.86 (1.56, 2.21)	1.91 (1.61, 2.26)	1.87 (1.57, 2.24)
Pack-years (for IQR, 10 pack-yrs)	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)
Blood lead (90th vs. 10th)	–	1.65 (1.32, 2.05)	–	–
Predicted tibia lead (90th vs. 10th)	–	–	4.81 (2.27, 10.2)	–
Predicted patella lead (90th vs. 10th)	–	–	–	3.03 (1.74, 5.29)

Cox proportional hazard regression was fit with time-on-study as the time scale.

association with all-cause mortality was weaker (HR = 1.25 (0.82–1.92) (Weisskopf et al., 2009). In the same study, BLLs were not associated with any mortality outcomes. In another study in the same cohort, all lead markers showed increased risks for developing ischemic heart disease but bone lead markers had greater risk compared to blood lead (HR = 2.64 (1.09–6.37), 1.84 (0.57–5.90), 1.45 (1.01–2.06) for every log-unit change in patella lead, tibia lead, and blood lead, respectively) (Jain et al., 2007). A meta-analysis based on 8 population-based studies concluded that tibia lead is associated with systolic blood pressure and hypertension risk (Navas-Acien et al., 2008). However, in a recent study using epigenetic biomarkers to estimate bone lead and BLLs among American Indian adults, the Strong Heart Study, the associations between bone lead and CVD mortality were not greater than that for blood lead (HRs per doubling increase = 1.42 (1.07–1.87) for estimated tibia lead; 1.22 (0.93–1.60) for estimated patella lead; 1.57 (1.16–2.11) for estimated blood lead) (Lieberman-Cribbin et al., 2022). Differences with the present study may be due to the Strong Heart Study using DNA methylation "signatures" to estimated blood and bone lead levels rather than the present study, which used measured BLLs and bone lead levels predicted from BLLs and other variables.

Our findings may also explain why low BLLs (even lower than 5 μg/dL) have been associated with elevated risk for cardiovascular mortality in the previous studies using NHANES data (Lanphear et al., 2018; Menke et al., 2006). BLLs in the US have declined since the phase-out of leaded gasoline starting from 1975. Geometric means of BLLs in adults were 13.1 μg/dL in the NHANES-II (1976–1980); 2.76 μg/dL in the NHANES-III (1988–1994); 1.64 μg/dL in the NHANES 1999–2002; and below 1 μg/dL in more recent NHANES cycles (Muntner et al., 2005; Pirkle et al., 1994; Wang et al., 2021). In studies with more recent NHANES data, low BLLs were significantly associated with cardiovascular mortality, for example, HR comparing the 75th vs the 25th percentiles of blood lead (2.44 vs. 1.10 μg/dL) was 1.45 (95 % CI: 1.21–1.74) (Wang et al., 2019). Although BLLs decline with cessation of external lead exposure, body burden of lead reflected as bone lead levels remains unchanged until bone turnover and mineral loss are accelerated and serves as endogenous sources of lead (Hu et al., 1998). The majority of adult participants of NHANES-III was born before 1980 and therefore, they had been exposed to high levels of airborne lead and thus were likely to have high cumulative lead even though their current BLLs did not look high. In the analytical sample in this study, over 80 % of the participants had BLLs <5 μg/dL. Even among those with BLLs <5 μg/dL, there were wide variations in predicted bone lead levels: predicted tibia lead and predicted patella lead levels ranged from −8.02 to 38.1 μg/g and 5.44 to 54.9 μg/g, respectively (Suppl Table S3). This suggests that a large number of US adults who were born before 1980 and thus were likely to be exposed to high lead in the past may be still at risk of cardiovascular toxicity from cumulative lead exposure.

We found larger HRs for CVD and heart disease mortality for predicted tibia lead compared to predicted patella lead (Table 2). This finding may indicate a difference in measurement error between tibia lead and patella lead as biomarkers of cumulative lead dose, rather than representing distinct lead toxicities based on the bone site. Lead in cortical bone (tibia lead) is considered a biomarker for long-term cumulative lead dose with decades of half-life, whereas lead in trabecular bone (patella lead) is less reliable as a biomarker for cumulative lead dose but is indicative of a higher level of bioavailable lead stores compared to tibia lead (Hu et al., 2007). The primary predictors identified for each predicted variable, age for tibia lead and blood lead for patella lead, further substantiate the prominent physiological differences between the two bone lead biomarkers (Wang et al., 2022).

Another notable finding is that the associations between lead markers and all-cause mortality were larger in non-Hispanic Black participants compared with non-Hispanic White participants. Although racial/ethnic differences in lead exposure have been well documented (Danziger et al., 2021; Teye et al., 2021; Theppeang et al., 2008; White et al., 2016), little is known about whether race/ethnicity plays a role in susceptibility to lead-related health effects, especially among adults. Hicken et al. found Black adults had significantly greater associations between blood lead and systolic blood pressure compared with White adults in the NHANES 2001–2008 (Hicken et al., 2012). Social disadvantage and psychosocial stress were suggested as driving factors for this Black-White disparity in the association between blood lead and high blood pressure (Hicken et al., 2012, 2013). Although we also found greater magnitudes in the association between lead markers and all-cause mortality in non-Hispanic Black compared with non-Hispanic White participants, this pattern was not observed in CVD mortality. On the other hand, lead markers were not associated with CVD mortality among Mexican Americans while both non-Hispanic White and non-Hispanic Black participants had significant positive associations. We are not aware of any studies evaluating the differences in effect of lead toxicity comparing Mexican Americans and other racial/ethnic groups. Hence, it is unclear whether the observed difference is real or a chance finding. It should be noted that BLLs in Mexican Americans were similar to those in non-Hispanic White participants (2.78 vs. 2.68 μg/dL, Suppl Table S4). It should also be noted that the bone lead prediction models were developed from a cohort of White male participants, the Normative Aging Study. Prediction performance for females and other race/ethnic groups cannot be ensured if the distributions of predictors included in the models are different by sex and race/ethnicity. This is why the results of sub-group analyses (e.g., Fig. 1) should be interpreted with caution and we cannot rule out that the observed racial/ethnic differences are due to differential prediction errors by subgroups.

There are several limitations that should be considered. First, as discussed above, the prediction models were developed within a racial/

ethnically homogeneous male population, while their utility was tested against a racial/ethnically diverse population encompassing both genders. Given the inherent tendency of these models to overestimate true bone lead concentrations when they are below average (Wang et al., 2022), and women typically possess lower bone lead concentrations than men, the predicted bone lead concentrations applied to the NHANES and the observed associations would be likely to be overestimated. Second, we used the models with predictors that are routinely collected in other population studies (except BLLs, which are typically not measured in non-environmental cohort studies) to increase the utility of the models. These models can be applied to other cohorts as long as whole blood samples (either at the time of collection, or archived) for blood lead assessment are available. The bone lead prediction performance may be improved with additional predictors such as DNA methylation markers (Colicino et al., 2021).

In conclusion, this study suggests that previous assessments of the cardiovascular mortality risk associated with lead exposure, which relied on BLLs as biomarkers, may have underestimated the true effects. Utilizing predicted bone lead variables as exposure markers could yield a more accurate estimation of the mortality risk. As the aging population grows as well as ongoing lead exposure from old infrastructure persists in urban communities, cardiovascular toxicity of cumulative lead exposure is likely to continue in the future. The present study adds to the importance of developing comprehensive strategies including reducing population-wide lead exposure, especially in environmentally disadvantaged communities, to prevent cardiovascular disease (Lanphear et al., 2018).

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CRediT authorship contribution statement

Sung Kyun Park: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **Xin Wang:** Investigation, Writing – review & editing. **Seulbi Lee:** Investigation, Writing – review & editing. **Howard Hu:** Conceptualization, Methodology, Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

We used NHANES data which is publicly available at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. Analytical data and R codes are available at https://github.com/um-mpeg/Bone-lead-mortality.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.171511.

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