A Prospective Study of Bone Lead Concentration and Death From All Causes, Cardiovascular Diseases, and Cancer in the Department of Veterans Affairs Normative Aging Study

Marc G. Weisskopf, PhD; Nitin Jain, MD; Huiling Nie, PhD; David Sparrow, DSc; Pantel Vokonas, MD; Joel Schwartz, PhD; Howard Hu, MD

Background—Blood lead concentration has been associated with mortality from different causes in several studies. Many effects of lead exposure that might increase risk of death are likely to result from cumulative exposure, for which bone lead is a better biomarker than blood lead. The association between bone lead levels and mortality has not been explored.

Methods and Results—We prospectively assessed the association between both blood lead and bone lead, analyzed with the use of K-shell x-ray fluorescence, and mortality among 868 men in the Normative Aging Study. We identified 241 deaths over an average of 8.9 (SD=3.9) years of follow-up. We calculated adjusted hazard ratios and 95% confidence intervals using Cox proportional hazards. Compared with the lowest tertile of patella bone lead, the fully adjusted hazard ratios in the highest tertile for all-cause, cardiovascular (n=137 deaths), and ischemic heart disease (n=62 deaths) mortality were 1.25 (95% confidence interval, 0.82 to 1.92), 1.42 (95% confidence interval, 0.80 to 2.51), and 1.87 (95% confidence interval, 0.77 to 4.53), respectively. Results were similar for tibia lead. Bone lead was not associated with cancer, and blood lead was not associated with any mortality category.

Conclusions—We found bone lead to be associated with a slight increase in all-cause and cardiovascular mortality in an environmentally exposed population with low blood lead levels, but this did not reach statistical significance. This study suggests that cumulative lead exposure from prior decades of high environmental exposures may affect risk of death despite recent declines in environmental lead exposure, but studies with more follow-up are needed. (Circulation. 2009;120:1056-1064.)

Key Words: environmental exposure ■ cardiovascular diseases ■ epidemiology ■ lead ■ mortality ■ population

The possibility that exposure to lead may contribute to cardiovascular disease is as old as Hippocrates and Vitruvius, who wrote that lead fumes “destroy the vigour of the blood.” Despite such ancient roots, the contribution of lead to cardiovascular disease is incompletely understood, although lead and other environmental contaminants are potentially modifiable risk factors for cardiovascular outcomes. Nonetheless, evidence that lead exposure is associated with a variety of adverse cardiovascular outcomes is growing, with the most extensive data being epidemiological studies relating it to increases in blood pressure and risk of hypertension. Controlled animal studies have confirmed these associations.

Clinical Perspective on p 1064

A few studies have reported an increased risk of cardiovascular mortality with increasing blood lead levels in data from both the second and third National Health and Nutrition Examination Surveys (NHANES). Lead in blood has a half-life of ≈30 days. In contrast, lead in bone—a major deposition site for lead in circulation and where the vast majority of lead in the body resides—has a half-life of many years to decades and thus is an indicator of cumulative exposure. Many of the known biological effects of lead on the cardiovascular system could be expected to exert their adverse effects chronically, and thus an indicator of cumulative exposure to lead would be expected to be a better biological marker of chronic toxicity.

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than blood lead. The association between bone lead concentration and mortality from cardiovascular or any other causes, however, has not been examined.

To address this issue, we followed participants in the Department of Veterans Affairs (VA) Normative Aging Study (NAS), a longitudinal study of aging among a cohort of community-dwelling elderly men from the greater Boston, Mass, area, who had previously had bone lead measurements taken with the use of K-shell x-ray fluorescence (KXRF). In a previous study of ours, we found an increased risk of primarily nonfatal (70 of 83 cases) ischemic heart disease with both increasing blood and bone lead levels.10 The present study, however, has longer follow-up, enabling us to look specifically at mortality.

Methods

Study Population

This research was conducted on a subgroup of the VA NAS, a multidisciplinary longitudinal study of aging in men established in 1963 when 2280 men from the Greater Boston area between the ages of 21 and 80 years were enrolled.11 Men with a history of treatment for hypertension, systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or other chronic conditions, including heart disease, diabetes mellitus, and cancer, were not admitted into the study. Study cohort members reported for medical examinations every 3 to 5 years, at which time extensive clinical and other health data were collected. The attrition rate for all causes has been <1% annually. From 1991 through 1999, 868 (68%) of 1283 active participants gave informed consent for a KXRF measurement of lead in bone. Of the participants with patella and tibia bone lead measurements, 8 and 5, respectively, were excluded because of high uncertainty values (see Bone Lead Measurements section below), leaving a final sample size of 860 for analyses of patella lead and 863 for tibia lead. Measurement of blood lead with the use of atomic absorption on fresh blood samples began in 1992. Of the active participants, 1235 (96%) provided blood for lead analysis. The research herein was approved by the Human Subjects Committees of the Boston VA Healthcare System, the Brigham and Women’s Hospital, and the Harvard School of Public Health.

Bone Lead Measurements

Bone lead measurements were taken at 2 anatomic sites, the mid tibial shaft (midpoint between the tibial plateau and the medial malleolus) and the patella, with an ABIOMED KXRF instrument (ABIOMED, Danvers, Mass) as described previously.12 Thirty-minute measurements were taken at each site, after each region had been washed with a 50% solution of isopropyl alcohol. The KXRF beam collimator was sited perpendicular to the flat bony surface of the tibia and at 30° in the lateral direction for the patella. We have previously found the correlation coefficient between KXRF and inductively coupled plasma mass spectrometry measurement of lead in cadaver bones to be 0.94 and 0.99 for tibia and patella bone, respectively.13 The average uncertainty around our typical KXRF measurements, equivalent to a standard deviation around the measurement, is ≈3 μg/g. Tibia (n=5) and patella (n=8) bone lead measurements with estimated uncertainties >10 and >15 μg/g bone, respectively, were excluded because these measurements usually reflect excessive participant movement during the measurement.

Blood Lead Measurements

Fresh blood for lead measurement was taken in a special lead-free tube containing EDTA and was sent to ESA Laboratories (Chelmsford, Mass). Blood samples were analyzed by Zeeman background-corrected flameless atomic absorption (graphite furnace). The instrument was calibrated before use with National Bureau of Standards Blood Lead Standard Materials. Ten percent of the samples were run in duplicate, 10% were controls, and 10% were blanks, analysis of which produced no evidence of external contamination or significant problems with reliability. In tests on reference samples from the Centers for Disease Control and Prevention, the coefficients of variation were 1% to 8%.

Case Ascertainment

Most deaths occurring in this cohort are notified through next of kin or postal authorities. Birthday cards and supplemental questionnaires mailed to participants provided additional opportunities to ascertain vital status and the records of the VA and the Social Security Administration Death Master File were also searched to pick up possible unreported deaths. Thus, we have nearly 100% mortality follow-up through March 2007. For participants who have died, death certificates are obtained from the appropriate state health department. These are reviewed by a board-certified cardiologist (P.V.) to assign cause of death codes according to the International Classification of Diseases, Ninth Revision (ICD-9). Cause-specific mortality was classified as cardiovascular disease (ICD-9 codes 390 to 459), ischemic heart disease (ICD-9 codes 410 to 414 and 429.2), other cardiovascular (no ICD-9 code of 410 to 414 or 429.2), and cancer (ICD-9 codes 140 to 239) on the basis of any underlying cause listed on the death certificate.

Covariates

Data on all covariates were obtained from the participants’ regularly collected NAS data at the time of the baseline lead measurement. We considered cigarette smoking both as status (never, former, current) and pack-years. Education was categorized into less than high school, high school graduate, vocational/trade school, some college, and completed college/graduate school. Race was coded as white or nonwhite. Alcohol intake was assessed with a food frequency questionnaire. Participants were asked how many servings per day they drank of beer, wine, and hard liquor, and these were converted to grams of alcohol per day. Responses were categorized into nondrinkers and then successive tertiles of grams per day among those who did drink alcohol. Physical activity was assessed with a modified Paffenbarger scale.14 NAS participants reported how many hours they walked weekly, how many flights of stairs they climbed daily, and the type, frequency, and duration of their participation in sports or recreational activities in hours per week. From these data, a physical activity index was computed in kilocalories per week, which we categorized into quartiles. Weight, height, and blood pressure were assessed by trained staff. The height and weight were used to calculate body mass index (weight in kilograms divided by the square of height in meters). Participants were...
considered to have hypertension if their systolic blood pressure was >140 mm Hg, their diastolic blood pressure was >90 mm Hg, or they reported having been diagnosed with hypertension by a physician. Blood samples were analyzed for total cholesterol and serum high-density lipoprotein. Participants were asked if they had been diagnosed with diabetes mellitus.

### Statistical Analyses

Participants contributed follow-up time from the date of their first blood or bone lead measurement for the blood lead and bone lead analyses, respectively, to the date of death or the date of their last contact with the NAS. Direct standardization by age was done for the descriptive statistics to minimize the influence of age (with which bone lead is strongly associated) on the distribution of covariates. The standardization was done by calculating a weighted average of the age-specific averages (continuous variables) or percentages (categorical variables) where the weights were the age-specific proportions (in 5-year groups) of our study population. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariable Cox models with age as the time metric were adjusted for age at XRF (in months), smoking (both status and pack-years) and education. Additional covariates considered in other models were alcohol intake, physical activity, body mass index, total cholesterol, serum high-density lipoprotein, diabetes mellitus, race, and hypertension. To ensure proper temporality and avoid the possibility that disease might alter exposure levels, we ran additional models excluding anyone with cardiovascular conditions or cancer, depending on the model, at baseline. Tests for linear trend across tertiles were computed by including tertile of lead biomarker as a continuous variable in the models. SAS version 9.1 was used for these analyses. We additionally tested for nonlinearity of the lead terms using Cox proportional hazards models in the R software package with penalized spline terms for the lead biomarkers.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

Compared with NAS participants with measurement of lead in blood but not bone, those with bone lead measurements more often had at least some college education (42% versus 36%) and were ever smokers (78% versus 70%). Otherwise, they were similar, including blood lead concentration (mean, 0.28 versus 0.26 μg/dL; 5.7 versus 5.3 μmol/L). Among the 860 NAS participants with valid patella bone lead measurements, we identified 241 deaths during 7673 person-years of follow-up, an average of 8.9 years per participant (SD=3.9). The men averaged 67.3 (SD=7.3) years of age at the baseline bone lead measurement. The average patella and tibia bone lead concentrations were 31.2 (SD=19.4) and 21.8 (SD=13.6) μg/g bone mineral, respectively. The average blood lead concentration measured at baseline (1994±3 years) was 0.27 (SD=0.16) μmol/L (5.6 [SD=3.4] μg/dL). The geometric mean of blood lead was 0.23 [interquartile range, 0.14 to 0.34] μmol/L (4.8 [interquartile range, 3 to 7] μg/dL). The Pearson correlation coefficient between patella bone lead and blood lead measured at the same time was 0.38 and between patella and tibia bone lead was 0.77. Participants with higher patella bone lead concentration at baseline were more likely to be nonwhite, smokers, and not have more than a high school education (Table 1). Those with higher patella lead concentrations also tended to be slightly less active, were slightly more likely to have hypertension, and were slightly less likely to have had a stroke. Those with higher patella lead concentrations also tended to be older (Table 1), although this trend reverses among the oldest participants. Among NAS participants aged <80 years at the time of bone lead measurement (n=825), the Spearman correlation between age and patella bone lead concentration was 0.27, whereas among those participants aged ≥80 years at the time of bone lead measurement (n=35), the Spearman correlation was −0.12.

The crude HR for all mortality end points except other cardiovascular deaths increased with increasing patella bone lead tertiles (Table 2). In age, smoking status, pack-years, and education-adjusted models, however, these trends were reduced. For all-cause, cardiovascular, and ischemic heart disease mortality, the associations were stronger in the multivariable model that excluded any participants who had ischemic heart disease or history of stroke at baseline. In this multivariable-adjusted model for ischemic heart disease mortality, the HR for those in the highest tertile of patella lead compared with the lowest was 1.87 (95% CI: 0.77–4.53). In the same multivariable-adjusted model for cardiovascular disease mortality, the HR in the highest compared with lowest tertile of patella lead was 1.42 (95% CI: 0.80–2.42). The multivariable HR for other cardiovascular deaths did not appear to increase with increasing bone lead. Additionally adjusting for hypertension or race in models of patella bone lead did not meaningfully change the results. Including alcohol, physical activity, body mass index, high-density lipoprotein, cholesterol, and diabetes mellitus in the model made the results for ischemic heart disease appear somewhat more monotonic for both the full multivariable model (HR for 2nd and 3rd tertile of 1.32 and 1.47, respectively) and the restricted multivariable model (HR for 2nd and 3rd tertile of 1.26 and 1.84, respectively). Results of other models were not materially changed with the additional adjustment. Cancer mortality did not exhibit an association with patella bone lead in multivariable models.

In spline regression models excluding participants with heart disease or stroke at baseline, the pattern of the tertile analyses is generally confirmed, except for ischemic heart disease mortality for which the spline suggests an association with increasing patella lead up to about 100 microg/g patella lead. Above this level the association is lost, although in this range the data were sparse and the CIs were wide (Figure). When the analysis is restricted to patella lead <100 microg/g, the spline suggests a linear increase in HR with increasing patella lead (p=0.07).

The multivariable model results for tibia lead and mortality were weaker than those for patella lead. In the age-, smoking-, and education-adjusted models excluding those with existing heart conditions, participants in the highest tertile of tibia lead compared with the lowest had an HR of 1.13 (95% CI: 0.73–1.75) for all-cause mortality, 1.26 (95% CI: 0.71–2.25) for cardiovascular disease mortality, and 1.08 (95% CI: 0.45–2.61) for...
for ischemic heart disease. For nonischemic heart disease, the association with tibia was slightly stronger than for patella as the HR in the highest quintile compared with the lowest was 1.40 (95% CI: 0.65-3.02).

Although crude associations between blood lead and mortality generally tended toward increasing mortality with increasing blood lead tertile, we did not see associations with blood lead in multivariable-adjusted models (Table 3). These analyses included 1243 NAS participants with blood lead measures, among whom we identified 327 deaths over 10090 person-years of follow-up. Furthermore, in analyses restricted to the subset of NAS participants for whom we had bone lead data in which both blood lead (at the time of the bone lead measurement) and bone lead tertiles were included in the model, there were still no associations with blood lead, and the associations with bone lead were effectively unchanged.

### Discussion

In this prospective study, we found no association between blood lead and cardiovascular mortality, but the suggestion of an increased risk with increasing patella bone lead. This was most suggestive for ischemic heart disease mortality, for which the risk increased with increasing patella lead up to about 100µg/g. Above 100µg/g the risk dropped precipitously, which may suggest some form of bias at these highest patella lead concentrations. A similar pattern, although weaker, was seen for all-cause and all cardiovascular death. These findings were among a population of men with blood lead levels only slightly higher than US averages for men of...
a similar age\(^1\) and likely well within the range that would be seen around the world, particularly in countries that banned leaded gasoline more recently than the United States or have not banned leaded gasoline at all.

Major strengths of our study include the prospectively followed community-dwelling cohort and having both blood and bone lead data. Bone lead levels provide a better indicator of cumulative exposure to lead than do blood lead levels because of the much longer half-life of lead in bone.\(^9\)

There are several limitations to this study that should be recognized. First, our study is restricted to men, the majority of whom are white. Thus, whether the results generalize to women or minorities remains a question. Additionally, bone lead measurements are not perfectly precise and are made with some error. This measurement error, however, is most likely unrelated to overall or cause-specific mortality and thus would be likely to bias results toward the null rather than to induce a spurious association. We also adjusted for several covariates that might confound the association between lead and cardiovascular mortality, but, as with any observational study, the possibility of residual confounding by these variables or confounding by other unmeasured variables cannot be completely ruled out. Although 32\% of active NAS participants did not participate in bone lead measurements, this group was generally similar to those who did, in particular in blood lead level, which suggests that little bias would be introduced from the lack of participation. Finally, in comparison to recent studies examining blood lead data in NHANES,\(^7,8\) the present study was substantially smaller. Overall, though, the fact that we still found suggestive associations between bone lead and mortality in a sample with >6 times fewer deaths suggests that bone lead is likely a better biomarker for these outcomes.

As in this study, bone lead has been found in other studies to be a stronger predictor than blood lead of several other health end points (eg, hypertension,\(^12,18,19\) ECG disturbances,\(^20\) pulse pressure,\(^21\) renal function,\(^22\) cognition,\(^23,24\) cataracts\(^25\)), and this suggests that this biomarker should be strongly

| Table 2. Hazard ratios (HR; 95% CI) for all-cause, cardiovascular disease, ischemic heart disease, other cardiovascular, and cancer mortality by tertile of patella lead at baseline |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Tertile of patella Pb**                        | 1 (<22 μg/g)    | 2 (22 to 35 μg/g) | 3 (>35 μg/g)    | **P for trend**  |
| **n**                                           | 298             | 283             | 279             |                  |
| **Follow-up, y**                                | 2763            | 2523            | 2387            |                  |
| **All-cause**                                    |                 |                 |                 |                  |
| **Deaths**                                      | 55              | 75              | 111             |                  |
| **Crude**                                        | Ref             | 1.36 (0.96–1.93) | 1.39 (1.00–1.94) | 0.07             |
| **Multivariable 1**                             | Ref             | 1.14 (0.80–1.64) | 1.11 (0.77–1.60) | 0.60             |
| **Multivariable 2†**                            | Ref             | 1.17 (0.77–1.78) | 1.25 (0.82–1.92) | 0.31             |
| **All-cardiovascular**                          |                 |                 |                 |                  |
| **Deaths**                                      | 33              | 41              | 63              |                  |
| **Crude**                                        | Ref             | 1.24 (0.78–1.97) | 1.27 (0.82–1.96) | 0.31             |
| **Multivariable 1**                             | Ref             | 1.06 (0.66–1.71) | 1.14 (0.71–1.83) | 0.59             |
| **Multivariable 2†**                            | Ref             | 1.04 (0.58–1.86) | 1.42 (0.80–2.51) | 0.21             |
| **Ischemic heart disease**                       |                 |                 |                 |                  |
| **Deaths**                                      | 14              | 18              | 30              |                  |
| **Crude**                                        | Ref             | 1.31 (0.65–2.65) | 1.58 (0.82–3.03) | 0.17             |
| **Multivariable 1**                             | Ref             | 1.07 (0.52–2.21) | 1.34 (0.66–2.74) | 0.40             |
| **Multivariable 2†**                            | Ref             | 1.08 (0.43–2.70) | 1.87 (0.77–4.53) | 0.14             |
| **Other cardiovascular**                        |                 |                 |                 |                  |
| **Deaths**                                      | 19              | 23              | 33              |                  |
| **Crude**                                        | Ref             | 1.18 (0.64–2.17) | 1.06 (0.59–1.90) | 0.90             |
| **Multivariable 1**                             | Ref             | 1.06 (0.56–1.99) | 1.00 (0.53–1.88) | 0.98             |
| **Multivariable 2†**                            | Ref             | 1.01 (0.48–2.16) | 1.12 (0.53–2.36) | 0.77             |
| **Cancer**                                      |                 |                 |                 |                  |
| **Deaths**                                      | 21              | 28              | 42              |                  |
| **Crude**                                        | Ref             | 1.37 (0.78–2.42) | 1.68 (0.98–2.87) | 0.06             |
| **Multivariable 1**                             | Ref             | 1.10 (0.61–1.97) | 1.19 (0.66–2.15) | 0.56             |
| **Multivariable 2†**                            | Ref             | 0.98 (0.48–2.01) | 1.13 (0.54–2.33) | 0.74             |

*Adjusted for age at XRF, smoking (never/former/current and pack-years), and education.
†Excluding the 154 subjects (53 deaths) who had heart disease (146) or stroke (11) at bone lead measurement.
‡Multivariable models of cancer excluding 133 participants (34 deaths) with cancer at baseline.
considered for monitoring environmental exposures relevant for health. Currently, blood lead is the only lead biomarker assessed in NHANES, and current Occupational Safety and Health Administration standards on exposure to lead relate only to blood lead. Bone lead, however, may be a more relevant biomarker and a more important indicator of subsequent health events, at least when the exposure assessment is done only once.

No previous studies have examined the association between bone lead and mortality, although several have reported associations with blood lead in data from NHANES. In the most recent studies from the third (1988–1994) NHANES, blood lead levels were associated with an increased rate of all-cause, cardiovascular, and, in the study not restricted to those with lower blood lead levels, cancer mortality. Among adults aged ≥20 years with blood lead concentrations <0.48 μmol/L (10 μg/dL), the HR for those with blood lead concentrations in the highest tertile (≥0.175 μmol/L [3.63 μg/dL]) was 25% higher than those with blood lead in the lowest tertile (<0.093 μmol/L [1.93 μg/dL]) for all-cause mortality and 55% higher for cardiovascular mortality.

Among adults aged ≥40 years, the HR for those with blood lead concentrations ≥0.48 μmol/L (10 μg/dL) was 59% higher than for those with blood lead <0.24 μmol/L (5 μg/dL) for all-cause mortality and 55% higher for cardiovascular mortality. The average age at baseline in 1 of these studies was >20 years younger than in the present study, which, given the difference from our findings for blood lead, could suggest that blood lead at earlier ages is more predictive than blood lead at older ages. The other recent article on blood lead, however, found associations even among older participants, although the findings appeared slightly less robust at older ages. In a study of primarily nonfatal ischemic heart disease (70 of 83 cases) in the NAS, however, both blood lead and patella bone lead were significantly associated with myocardial infarction or angina pectoris, although patella lead appeared to be the stronger predictor. Three prior studies with only blood lead data, however, did not find an association with that biomarker.

An alternative explanation for the differences in findings for blood lead in our cohort and the NHANES studies is that if exposures to lead in the Greater Boston area were more varied at the time of blood lead assessment than they were for the more national NHANES cohorts (as is possibly suggested by the slightly higher blood lead levels in our cohort), this could result in more fluctuation in blood lead levels. If this were the case, then any single blood lead measure would be less correlated with overall lead exposure in our cohort and show a reduced effect estimate for mortality if it is truly cumulative exposure that is important for mortality outcomes.

There are several mechanisms by which exposure to lead may result in cardiovascular mortality in particular (for review, see Navas-Acien et al). Lead can have direct effects on the excitability and contractility of the heart and increase vascular tone and peripheral resistance via effects such as stimulation of the renin-angiotensin system, reduction in nitric oxide availability and guanylate cyclase, or increase in oxidative stress. Lead has been found to induce proliferation of vascular smooth cells and fibroblasts and induce atherosclerosis in animal models. In addition, neurotoxic effects of lead can affect autonomic control of the heart. The most extensive data in humans relate to the association between lead exposure and higher blood pressure or hypertension, but lead exposure has also been associated with many other cardiovascular end points, including pulse pressure (an indicator of arterial stiffening), ECG disturbances, and ischemic heart disease in this same cohort. The association with heart disease deaths was similar after control for blood pressure, suggesting that...
other mechanisms likely mediate the effect of lead on heart disease. Given the mechanisms of these effects of lead on the cardiovascular system, it is not surprising that a cumulative biomarker of lead exposure, such as bone lead, would be a better predictor of cardiovascular mortality than blood, which is a more acute exposure biomarker.

Cardiovascular disease is the leading cause of death in the United States and one of the most significant contributors to mortality worldwide.\textsuperscript{37,38} Projections of future trends in cardiovascular mortality have important healthcare planning implications. Cardiovascular mortality has generally shown a steady decrease over the past several decades in developed countries, although the opposite is seen in some developing countries.\textsuperscript{37,39,40} These trends tend to be paralleled by trends in traditional cardiovascular risk factors such as blood pressure, cholesterol levels, and smoking.\textsuperscript{41,42} These trends, however, do not explain all the change in cardiovascular mortality, and, at least in some cases, cardiovascular mortality continues to decline despite a leveling off of changes in traditional risk factors.\textsuperscript{42} Lead exposure has not been considered in this equation, but in the United States and many other developed countries, environmental exposures have been declining since the mid-1970s.\textsuperscript{43} These declines may well have contributed to declining cardiovascular mortality rates. Because of the long residence time of lead in bone, a storage site from which it can later reenter circulation,\textsuperscript{9} and the aging of the population, the full effects of reducing environmental levels of lead may continue for some time.

In summary, we found that in a population of community-dwelling elderly men with biomarkers of both blood and bone lead, there was a suggestion that bone lead, but not blood lead, was associated with an increased mortality rate that was more apparent for cardiovascular disease and specifically between patella lead and ischemic heart disease.

### Table 3. Hazard ratios (HR; 95% CI) for all-cause, cardiovascular disease, ischemic heart disease, other cardiovascular, and cancer mortality by tertile of blood lead at baseline

<table>
<thead>
<tr>
<th>Tertile of blood Pb</th>
<th>n</th>
<th>Follow-up, y</th>
<th>All-cause Deaths</th>
<th>Crude</th>
<th>Multivariable 1*</th>
<th>Multivariable 2†</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0.19 (\mu)mol/L) (&lt;4 (\mu)g/dL)</td>
<td>322</td>
<td>2763</td>
<td>72</td>
<td>Ref</td>
<td>1.04 (0.78–1.38)</td>
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<td>2 (0.19–0.29 (\mu)mol/L) (4–6 (\mu)g/dL)</td>
<td>565</td>
<td>4444</td>
<td>145</td>
<td>Ref</td>
<td>0.98 (0.73–1.31)</td>
<td>0.97 (0.71–1.32)</td>
<td>0.84</td>
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<tr>
<td>3 (&gt;0.29 (\mu)mol/L) (&gt;6 (\mu)g/dL)</td>
<td>356</td>
<td>2883</td>
<td>110</td>
<td>Ref</td>
<td>0.99 (0.71–1.37)</td>
<td>1.01 (0.71–1.44)</td>
<td>0.92</td>
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### All-cause

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<th>Tertile of blood Pb</th>
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<td>565</td>
<td>4444</td>
<td>145</td>
<td>Ref</td>
<td>1.09 (0.74–1.60)</td>
<td>1.09 (0.72–1.66)</td>
<td>0.71</td>
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<tr>
<td>3 (&gt;0.29 (\mu)mol/L) (&gt;6 (\mu)g/dL)</td>
<td>356</td>
<td>2883</td>
<td>110</td>
<td>Ref</td>
<td>1.09 (0.69–1.72)</td>
<td>1.10 (0.67–1.80)</td>
<td>0.72</td>
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### Ischemic heart disease

<table>
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<tr>
<th>Tertile of blood Pb</th>
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<th>Follow-up, y</th>
<th>All-cause Deaths</th>
<th>Crude</th>
<th>Multivariable 1*</th>
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</thead>
<tbody>
<tr>
<td>1 (&lt;0.19 (\mu)mol/L) (&lt;4 (\mu)g/dL)</td>
<td>17</td>
<td>36</td>
<td>17</td>
<td>Ref</td>
<td>1.13 (0.63–2.01)</td>
<td>1.32 (0.72–2.41)</td>
<td>0.35</td>
</tr>
<tr>
<td>2 (0.19–0.29 (\mu)mol/L) (4–6 (\mu)g/dL)</td>
<td>36</td>
<td>63</td>
<td>29</td>
<td>Ref</td>
<td>1.03 (0.57–1.86)</td>
<td>1.11 (0.60–2.07)</td>
<td>0.72</td>
</tr>
<tr>
<td>3 (&gt;0.29 (\mu)mol/L) (&gt;6 (\mu)g/dL)</td>
<td>85</td>
<td>110</td>
<td>63</td>
<td>Ref</td>
<td>1.10 (0.54–2.23)</td>
<td>1.21 (0.57–2.55)</td>
<td>0.61</td>
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</table>

### Other cardiovascular

<table>
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<tr>
<th>Tertile of blood Pb</th>
<th>n</th>
<th>Follow-up, y</th>
<th>All-cause Deaths</th>
<th>Crude</th>
<th>Multivariable 1*</th>
<th>Multivariable 2†</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0.19 (\mu)mol/L) (&lt;4 (\mu)g/dL)</td>
<td>21</td>
<td>49</td>
<td>21</td>
<td>Ref</td>
<td>1.13 (0.68–1.89)</td>
<td>1.05 (0.61–1.83)</td>
<td>0.91</td>
</tr>
<tr>
<td>2 (0.19–0.29 (\mu)mol/L) (4–6 (\mu)g/dL)</td>
<td>49</td>
<td>74</td>
<td>34</td>
<td>Ref</td>
<td>1.12 (0.67–1.88)</td>
<td>1.05 (0.60–1.86)</td>
<td>0.90</td>
</tr>
<tr>
<td>3 (&gt;0.29 (\mu)mol/L) (&gt;6 (\mu)g/dL)</td>
<td>85</td>
<td>110</td>
<td>63</td>
<td>Ref</td>
<td>1.09 (0.60–1.98)</td>
<td>1.01 (0.53–1.94)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### Cancer

<table>
<thead>
<tr>
<th>Tertile of blood Pb</th>
<th>n</th>
<th>Follow-up, y</th>
<th>All-cause Deaths</th>
<th>Crude</th>
<th>Multivariable 1*</th>
<th>Multivariable 2†</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (&lt;0.19 (\mu)mol/L) (&lt;4 (\mu)g/dL)</td>
<td>28</td>
<td>57</td>
<td>28</td>
<td>Ref</td>
<td>1.08 (0.69–1.71)</td>
<td>1.12 (0.69–1.81)</td>
<td>0.67</td>
</tr>
<tr>
<td>2 (0.19–0.29 (\mu)mol/L) (4–6 (\mu)g/dL)</td>
<td>57</td>
<td>85</td>
<td>40</td>
<td>Ref</td>
<td>0.99 (0.62–1.56)</td>
<td>0.93 (0.57–1.53)</td>
<td>0.77</td>
</tr>
<tr>
<td>3 (&gt;0.29 (\mu)mol/L) (&gt;6 (\mu)g/dL)</td>
<td>85</td>
<td>110</td>
<td>63</td>
<td>Ref</td>
<td>1.01 (0.60–1.69)</td>
<td>0.48 (0.25–0.91)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Adjusted for age at XRF, smoking (never/former/current and pack-years), and education.
†Excluding the 214 subjects (73 deaths) who had heart disease (203) or stroke (12) at bone lead measurement.
‡Multivariable models of cancer excluding 198 participants (40 deaths) with cancer at baseline.

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None.

Disclosures

References

Genetics is well known to play only a limited role in the pathogenesis of cardiovascular disease. It is now known that in addition to diet, exercise, and other lifestyle and behavioral factors, certain environmental risk factors play a significant role in the general population. Much attention has been paid recently to particulate air pollution and secondhand cigarette smoke as such risk factors, for example. This study builds on another body of research recently indicating that cumulative environmental lead exposure (from decades of exposures to lead in combusted gasoline, paint, water, and food cans) is a risk factor for hypertension and myocardial infarction and goes even farther by suggesting that such exposure may increased prospective cardiovascular mortality. Like a number of other recent studies, this investigation also shows that the risk to individuals posed by lead exposure cannot be captured adequately by measuring blood lead levels, which primarily signifies recent, rather than cumulative, exposure. From a clinical perspective, this research highlights the importance of incorporating at least a brief environmental/occupational assessment in the conduct of preventive cardiology and medicine and of advocating for the elimination or minimization of activities that are associated with lead exposure. It also underscores the anticipation surrounding an ongoing National Institutes of Health–funded multicenter trial testing the potential value of chelation in reducing cardiovascular risks, the results of which remain pending.
A Prospective Study of Bone Lead Concentration and Death From All Causes, Cardiovascular Diseases, and Cancer in the Department of Veterans Affairs Normative Aging Study
Marc G. Weisskopf, Nitin Jain, Huiling Nie, David Sparrow, Pantel Vokonas, Joel Schwartz and Howard Hu

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In the article by Weisskopf et al, “A Prospective Study of Bone Lead Concentration and Death From All Causes, Cardiovascular Diseases, and Cancer in the Department of Veterans Affairs Normative Aging Study,” which published online September 8, 2009, and appeared with the September 22, 2009, issue of the journal (Circulation. 2009; 120:1056–1064), a correction was needed.

In trying to adjust finely for age at bone lead measurement the models were stratified on age at lead measurement in months, which resulted in over-stratification and the inadvertent exclusion of many participants. In order to include all participants, the analyses were modified without stratification, age was used as the time metamer, and the data were adjusted for age at bone lead measurement in the model instead. While a somewhat similar pattern is seen, particularly for patella lead and ischemic heart disease mortality, the results do not reach statistical significance. There is still no association with blood lead.

The authors regret the errors. The corrections have been made to the current online version of the article.