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Circulation. 2006;114:1388-1394; originally published online September 18, 2006;
doi: 10.1161/CIRCULATIONAHA.106.628321
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Blood Lead Below 0.48 μmol/L (10 μg/dL) and Mortality Among US Adults

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Background—Blood lead levels above 0.48 μmol/L (10 μg/dL) in adults have been associated with increased risk of cardiovascular, cancer, and all-cause mortality. The objective of the present study was to determine the association between blood lead levels below 0.48 μmol/L and mortality in the general US population.

Methods and Results—Blood lead levels were measured in a nationally representative sample of 13 946 adult participants of the Third National Health and Nutrition Examination Survey recruited in 1988 to 1994 and followed up for up to 12 years for all-cause and cause-specific mortality. The geometric mean blood lead level in study participants was 0.12 μmol/L (2.58 μg/dL). After multivariate adjustment, the hazard ratios (95% CI) for comparisons of participants in the highest tertile of blood lead (≥0.17 μmol/L [≥3.62 μg/dL]) with those in the lowest tertile (<0.09 μmol/L [<1.94 μg/dL]) were 1.25 (1.04 to 1.51; P_{trend} across tertiles=0.002) for all-cause mortality and 1.55 (1.08 to 2.24; P_{trend} across tertiles=0.003) for cardiovascular mortality. Blood lead level was significantly associated with both myocardial infarction and stroke mortality, and the association was evident at levels >0.10 μmol/L (≥2 μg/dL). There was no association between blood lead and cancer mortality in this range of exposure.

Conclusions—The association between blood lead levels and increased all-cause and cardiovascular mortality was observed at substantially lower blood lead levels than previously reported. Despite the marked decrease in blood lead levels over the past 3 decades, environmental lead exposures remain a significant determinant of cardiovascular mortality in the general population, constituting a major public health problem. (***Circulation*. 2006;114:1388-1394.**)

Key Words: risk factors ■ mortality ■ cardiovascular diseases ■ myocardial infarction ■ stroke

Blood lead levels above 1.93 μmol/L (40 μg/dL) have been associated with increased risks of cardiovascular, cancer, and all-cause mortality in several occupational cohorts. In the general population, Lustberg and Silbergeld[1] also reported significant relationships between blood lead levels above 0.48 μmol/L (10 μg/dL) and cardiovascular, cancer, and all-cause mortality.

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Environmental lead exposures in the United States have generally declined since the mid-1970s, largely because of the phase-out of lead in gasoline, which was finalized in 1996. In addition, lead-based paints were restricted in use, and a voluntary program removed lead solder from food cans.[2,3] Among US adults, the geometric mean blood lead level decreased from 0.63 μmol/L (13.1 μg/dL) in 1976 to 1980 to 0.08 μmol/L (1.6 μg/dL) in 1999 to 2002. Currently, 99% of US adults have blood lead levels below 0.48 μmol/L (10 μg/dL).[2] To the best of our knowledge, the association of blood lead levels below 0.48 μmol/L (10 μg/dL) with mortality end points has never been investigated.

The purpose of the present analysis was to evaluate the association of blood lead levels below 0.48 μmol/L (10 μg/dL) with all-cause and cause-specific mortality in the general US population. To do so, we analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) Mortality Study, a cohort study based on a nationally representative sample of US adults in which blood lead was measured in 1988 to 1994, with participants followed up for up to 12 years.

Methods

Study Population

NHANES III was a stratified, multistage probability survey designed to select a representative sample of the civilian, noninstitutionalized US population.[4] Overall, 18 629 adults 20 years of age and older completed the NHANES III interview and examination between 1988 and 1994. After the exclusion of 2482 participants who were missing data for blood lead, 707 participants with blood lead ≥0.48 μmol/L (10 μg/dL), and 1494 participants who were missing other

Received March 20, 2006; revision received June 13, 2006; accepted July 6, 2006.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.106.628321**

study covariates, 13 946 NHANES III participants were available for the present analysis. The present study used a cohort design to evaluate the association between blood lead levels in adult NHANES III participants with their mortality through December 31, 2000.

The protocol for NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. All participants gave informed consent.

Baseline Data Collection

NHANES III baseline data were collected during an in-home interview and a subsequent visit to a mobile examination center. During the in-home interview, demographic information, including age, race-ethnicity, and sex, was collected with a standardized questionnaire. Additional data collected during the in-home interview included urban residence, education, household income, physical activity, cigarette smoking, alcohol consumption, current medication use, menopausal status for women, and history of diabetes mellitus, myocardial infarction, stroke, and/or cancer.

Blood pressure was measured 3 times during the in-home interview and 3 additional times during the visit to the mobile examination center. All blood pressure measurements for each participant were averaged, and hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or current use of blood pressure–lowering medication. Height and weight were measured, and body mass index was calculated as weight in kilograms divided by height in meters squared.

Participants had a blood specimen drawn from their antecubital vein by a trained phlebotomist according to a standardized protocol. Serum C-reactive protein (CRP) was quantified by latex-enhanced nephelometry. Participants were classified as having CRP <3.0 mg/L, between 3.0 and 9.9 mg/L, or ≥10.0 mg/L. Plasma glucose was measured by an enzymatic reaction. Diabetes mellitus was defined as a fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL), a nonfasting plasma glucose ≥11.1 mmol/L (≥200 mg/dL), or a self-reported history of diabetes mellitus with concurrent use of antidiabetic medication. Total serum cholesterol was measured enzymatically. Serum creatinine was measured by the Jaffe modified kinetic method. Glomerular filtration rate (GFR) was estimated with the Modification of Diet and Renal Disease equation after we aligned the serum creatinine concentrations with the assay used in the development of the equation.[5,6] Individuals were classified as having an estimated GFR ≥90, 60 to 89, or <60 mL · min^{-1} · 1.73 m^{-2}.

A detailed description of the methods used in the measurement of blood lead levels is available elsewhere.[7] All materials used for collecting and processing blood lead specimens were screened for possible lead contamination. Blood specimens for lead measurement were shipped on dry ice to the NHANES laboratory at the National Centers for Environmental Health at the Centers for Diseases Control and Prevention in Atlanta, Ga. Blood lead was measured by graphite furnace atomic absorption spectrophotometry as described by Sassa and colleagues.[8] The detection limit was 0.05 μmol/L (1.0 μg/dL). For 8.1% of study participants with lead levels below the detection limit, we imputed a level of 0.03 μmol/L (0.7 μg/dL). The analytical laboratory followed extensive quality control procedures.[7] To ensure accurate measurements of blood lead, blinded quality control pools were incorporated with NHANES III participants' samples. This program was incorporated for the entirety of NHANES III (ie, from 1988 through 1994). On the basis of these quality control data, no drift in blood lead occurred because of measurement error.

Mortality Follow-Up

NHANES III participants aged ≥17 years at baseline were followed up for mortality through December 31, 2000. The method of probabilistic matching was used to link NHANES III participants with the National Death Index to ascertain vital status and cause of death. Matching was based on 12 identifiers for each participant (eg, Social Security number, sex, and date of birth). Identical matching methodology applied to the NHANES I Epidemiological Follow-up Study for validation purposes found that 96.1% of deceased participants and 99.4% of living participants were classified correctly.

Cause of death was determined by the underlying cause listed on death certificates. The International Classification of Diseases (ICD) revision 9 (ICD-9) was used for deaths that occurred between 1988 and 1998, and ICD revision 10 (ICD-10) was used for deaths during 1999 and 2000. Cause-specific mortality was categorized as cardiovascular disease (ICD-9 codes 390 to 434 and 436 to 459; ICD-10 codes I00-I99), myocardial infarction (ICD-9 codes 410 to 414 and 429.2; ICD-10 codes I20-I25), stroke (ICD-9 codes 430 to 434 and 436 to 438; ICD-10 codes I60-I69), cancer (ICD-9 codes 140 to 239; ICD-10 codes C00-C97 and D00-D48), and lung cancer (ICD-9 codes 162.2 to 162.9; ICD-10 code C34).

Statistical Methods

Participants were categorized into blood lead tertiles based on the weighted population distribution. Baseline covariate levels were calculated by tertile of blood lead level after standardization to the age, race-ethnicity, and sex distribution of the US population. Age-, race-ethnicity–, and sex-standardized differences in baseline covariates across tertiles of lead were evaluated by linear regression for continuous variables and logistic regression for dichotomous variables.

For cohort analysis of the association between blood lead and mortality, follow-up for each study participant was calculated as the time between their NHANES III examination and the date of death, the date on which they turned 90 years of age, or December 31, 2000, whichever occurred first. The hazard ratios and 95% CIs of all-cause, cardiovascular, myocardial infarction, stroke, and cancer mortality associated with each tertile of lead level compared with the first tertile were calculated by Cox regression. Initial models were adjusted for age, race-ethnicity, and sex. Subsequent models were further adjusted for urban residence, cigarette smoking, alcohol consumption, education, physical activity, household income, menopausal status for women, body mass index, CRP, total cholesterol, and diabetes mellitus. Additional models were further adjusted for hypertension and GFR category, which are potential intermediate factors in the causal pathway between lead exposure and mortality. Tests for linear trend across tertiles of blood lead were computed by including tertile of lead as a continuous variable in the Cox regression models. Sensitivity analyses were conducted after exclusion of participants with a history of cardiovascular disease or cancer.

To further explore the dose–response relationship of blood lead level with mortality, we used restricted quadratic splines with knots at the 10th, 50th, and 90th percentiles of the blood lead distribution (0.05 μmol/L [1.00 μg/dL], 0.13 μmol/L [2.67 μg/dL], and 0.29 μmol/L [5.98 μg/dL], respectively). Finally, the association between blood lead as a continuous variable and mortality was determined overall and for subgroups defined by age, race-ethnicity, sex, menopausal status, urban and rural residence, cigarette smoking, overweight, diabetes mellitus, hypertension, and level of estimated GFR. For analyses that included blood lead level as a continuous variable, lead was log-transformed owing to its skewness, and the hazard ratios of mortality end points are presented for a 3.4-fold increase in blood lead. This increase corresponds to the difference between the 80th and 20th percentiles of the blood lead distribution (0.24 μmol/L [4.92 μg/dL] versus 0.07 μmol/L [1.46 μg/dL], respectively). The proportionality assumptions of the Cox models were evaluated with Schoenfeld residuals. Data were analyzed with SUDAAN (version 9.0; Research Triangle Institute, Research Triangle Park, NC) to account for the complex NHANES sampling design, which included unequal probabilities of selection, oversampling, and nonresponse.

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

The geometric mean blood lead level in study participants was 0.12 μmol/L [2.58 μg/dL]. Participants with higher lead levels were more likely to be older, non-Hispanic black or

TABLE 1. Baseline Characteristics Overall and Standardized by Age, Race-Ethnicity, and Sex by Tertile of Blood Lead

	Overall Crude	Tertile 1 (<0.09 μmol/L or <1.93 μg/dL)	Tertile 2 (0.09-0.17 μmol/L or 1.94–3.62 μg/dL)	Tertile 3 (≥0.18 μmol/L or ≥3.63 μg/dL)	P_{trend}
Age, y	44.4 (0.5)	36.7	45.4	50.7	<0.001
Male sex, %	47.0 (0.5)	22.9	49.1	68.7	<0.001
Non-Hispanic white, %	78.0 (1.2)	82.2	78.5	72.3	<0.001
Non-Hispanic black, %	9.8 (0.6)	7.4	9.3	13.5	<0.001
Mexican American, %	5.0 (0.4)	4.0	5.0	6.2	0.006
Postmenopause (among women), %	40.2 (1.4)	38.2	40.6	43.3	<0.001
High school education, %	76.3 (1.0)	81.5	77.7	70.7	<0.001
Household income <$20 000 per annum, %	32.2 (1.1)	28.2	31.0	37.3	<0.001
Urban residence, %	48.2 (4.7)	45.3	48.9	50.3	0.301
Current smoking, %	27.6 (0.8)	14.4	27.6	43.3	<0.001
Alcohol consumption, %	54.7 (1.5)	45.4	55.1	63.3	<0.001
Exercise, %	50.9 (1.3)	52.8	52.1	47.7	0.030
Body mass index, kg/m^2	26.6 (0.1)	26.8	26.7	26.1	0.002
Hypertension, %	23.3 (0.8)	22.1	23.2	24.0	0.091
Diabetes mellitus, %	5.5 (0.3)	6.7	6.0	4.5	<0.001
Total cholesterol, mg/dL	204.0 (0.8)	200.2	203.9	207.6	<0.001
Elevated CRP, %	7.6 (0.4)	8.8	7.1	6.8	0.007
Estimated GFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, %	4.5 (0.3)	3.4	4.4	5.1	0.004
History of cardiovascular disease, %	4.8 (0.3)	3.8	4.8	5.1	0.027
History of cancer, %	3.9 (0.2)	3.3	4.1	4.0	0.278

Mexican American, and male (Table 1). Among women, those who were postmenopausal were more likely to have higher lead levels. Also, those with higher lead levels were more likely to have a household income <$20 000, to be a current smoker, and to consume alcohol and were less likely to have a high school education and to exercise 3 or more times per week. Mean total cholesterol, the prevalence of hypertension, the prevalence of reduced GFR, and the prevalence of a history of cardiovascular disease were higher at higher lead levels. In contrast, mean body mass index and the prevalence of diabetes mellitus and elevated CRP were lower at higher blood lead levels.

Blood lead levels were associated with increased all-cause mortality (Table 2). The multivariate adjusted hazard ratio of all-cause mortality for the highest versus the lowest tertile was 1.25 (95% CI 1.04 to 1.51; P_{trend} across tertiles=0.002). When cause-specific deaths were investigated, the increased mortality was concentrated in cardiovascular deaths. The multivariate adjusted hazard ratios for the highest versus the lowest tertile of lead level were 1.55 (1.08 to 2.24), 1.89 (1.04 to 3.43), and 2.51 (1.20 to 5.26), respectively, for cardiovascular, myocardial infarction, and stroke mortality (each P_{trend} <0.05). In contrast, blood lead was not associated with the risk of cancer mortality in this range (Table 2). For lung cancer, the multivariate adjusted hazard ratios for the middle and highest tertiles versus the lowest tertile were 0.70 (0.34 to 1.42) and 0.79 (0.40 to 1.58). In spline regression models, the increase in all-cause and cardiovascular deaths was evident at blood lead levels >0.10 μmol/L (2.0 μg/dL; Figure 1).

After multivariate adjustment, the hazard ratio (95% CI) for a 3.4-fold increase in blood lead level was 1.34 (1.16 to 1.54) for all-cause mortality, 1.53 (1.21 to 1.94) for cardiovascular mortality, 1.78 (1.18 to 2.67) for myocardial infarction mortality, and 1.59 (1.08 to 2.34) for stroke mortality. The results were markedly consistent across subgroups. All-cause and cardiovascular mortality were positively associated with higher lead levels in all subgroups, and no significant interactions were present (Figure 2; all probability values for interaction >0.05).

Discussion

In this large, population-based prospective study, we identified a direct association between higher blood lead and increased mortality at substantially lower blood lead levels than reported previously. Indeed, an increased risk of cardiovascular, myocardial infarction, and stroke mortality was evident at blood lead levels >0.10 μmol/L (2.0 μg/dL). This increased mortality affected non-Hispanic whites, non-Hispanic blacks, and Mexican Americans and both males and females. In contrast, there was no increased cancer mortality risk at these ranges of exposure. The finding of no increased cancer mortality risk in the present study is consistent with experimental evidence in which increased numbers of tumors are induced in rodents only after relatively high doses.

In the occupational setting, blood lead levels above 1.93 μmol/L (40 μg/dL) have been repeatedly demonstrated to be associated with increased risk of elevated blood pressure, impaired renal function, and cancer. Using data from the NHANES II Mortality Follow-Up Study, including follow-up from 1976 through 1992, Lustberg and Silbergeld[1] also identified a significant association between blood lead levels

TABLE 2. Hazard Ratios (95% CIs) of All-Cause, Cardiovascular Disease, Myocardial Infarction, Stroke, and Cancer Mortality Associated With Tertile of Lead

	Tertile 1 (<0.09 μmol/L or <1.93 μg/dL)	Tertile 2 (0.09–0.17 μmol/L or 1.94–3.62 μg/dL)	Tertile 3 (≥0.18 μmol/L or ≥3.63 μg/dL)	P_{trend}
All-cause mortality, n	252	470	939	
Age, race-ethnicity, and sex adjusted	1.00	0.97 (0.76–1.23)	1.37 (1.15–1.64)	<0.001
Multivariable 1 adjusted*	1.00	0.93 (0.73–1.19)	1.30 (1.08–1.56)	<0.001
Multivariable 2 adjusted†	1.00	0.91 (0.72–1.15)	1.25 (1.04–1.51)	0.002
Cardiovascular disease mortality, n	104	219	443	
Age, race-ethnicity, and sex adjusted	1.00	1.01 (0.68–1.51)	1.51 (1.07–2.14)	0.004
Multivariable 1 adjusted*	1.00	1.06 (0.70–1.60)	1.64 (1.14–2.35)	0.001
Multivariable 2 adjusted†	1.00	1.03 (0.69–1.55)	1.55 (1.08–2.24)	0.003
Myocardial infarction mortality, n	50	83	234	
Age, race-ethnicity, sex adjusted	1.00	0.99 (0.55–1.79)	1.70 (0.99–2.90)	0.011
Multivariable 1 adjusted*	1.00	1.05 (0.56–1.97)	2.01 (1.12–3.61)	0.003
Multivariable 2 adjusted†	1.00	1.02 (0.55–1.89)	1.89 (1.04–3.43)	0.007
Stroke mortality, n	22	56	63	
Age, race-ethnicity, sex adjusted	1.00	1.89 (0.80–4.48)	2.04 (1.13–3.67)	0.017
Multivariable 1 adjusted*	1.00	2.23 (0.89–5.60)	2.61 (1.24–5.49)	0.013
Multivariable 2 adjusted†	1.00	2.19 (0.87–5.53)	2.51 (1.20–5.26)	0.017
Cancer mortality, n	67	106	238	
Age, race-ethnicity, sex adjusted	1.00	0.78 (0.50–1.22)	1.28 (0.96–1.71)	0.010
Multivariable 1 adjusted*	1.00	0.72 (0.46–1.13)	1.08 (0.81–1.45)	0.130
Multivariable 2 adjusted†	1.00	0.72 (0.46–1.12)	1.10 (0.82–1.47)	0.101

*Adjustment included age, race-ethnicity, sex, diabetes mellitus, body mass index, current or former smoking, alcohol consumption, physical activity, low income, CRP, total cholesterol, high school education, urban residence, and postmenopausal status.

†Adjustment includes variables in model 1, hypertension, and level of kidney function.

Sample sizes (n) refer to the number of events.

>0.48 μmol/L (10 μg/dL) and all-cause, cardiovascular, and cancer mortality. Blood lead levels in adults at the time of NHANES II (geometric mean 0.63 μmol/L [13.1 μg/dL]) were considerably higher than those in NHANES III.[3] As a consequence, the association between blood lead and mortality was not evaluated over the blood lead range investigated in the present study. In the British Regional Heart Study, blood lead levels were nonsignificantly higher in incident cases of ischemic heart disease and stroke than in noncases, although the number of events was smaller (n=316 and 66 cases of ischemic heart disease and stroke, respectively) than in the NHANES studies.[9] The average blood lead level in the

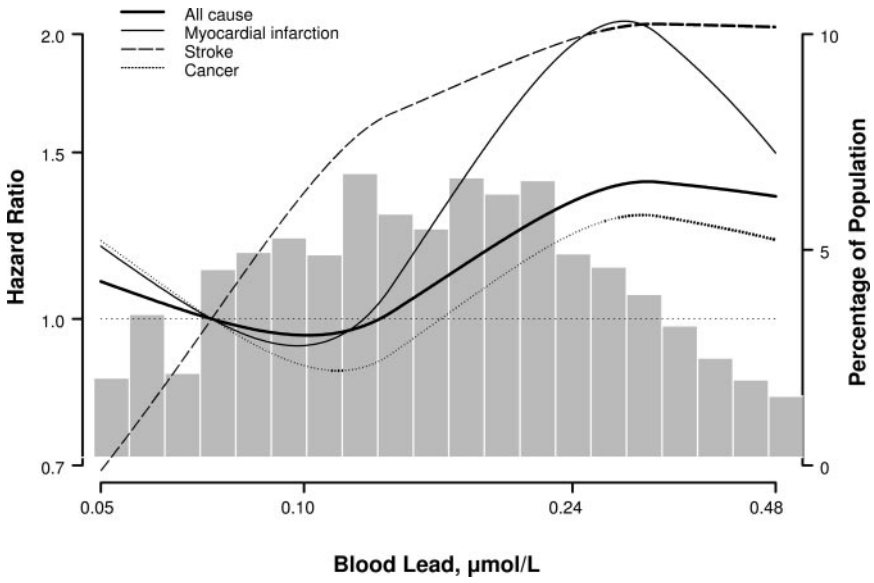

Figure 1. Multivariate adjusted relative hazard (left axis) of mortality associated with blood lead levels between 0.05 μmol/L (1 μg/dL) and 0.48 μmol/L (10 μg/dL). Histogram of blood lead levels is superimposed in the background and displayed on the right axis.

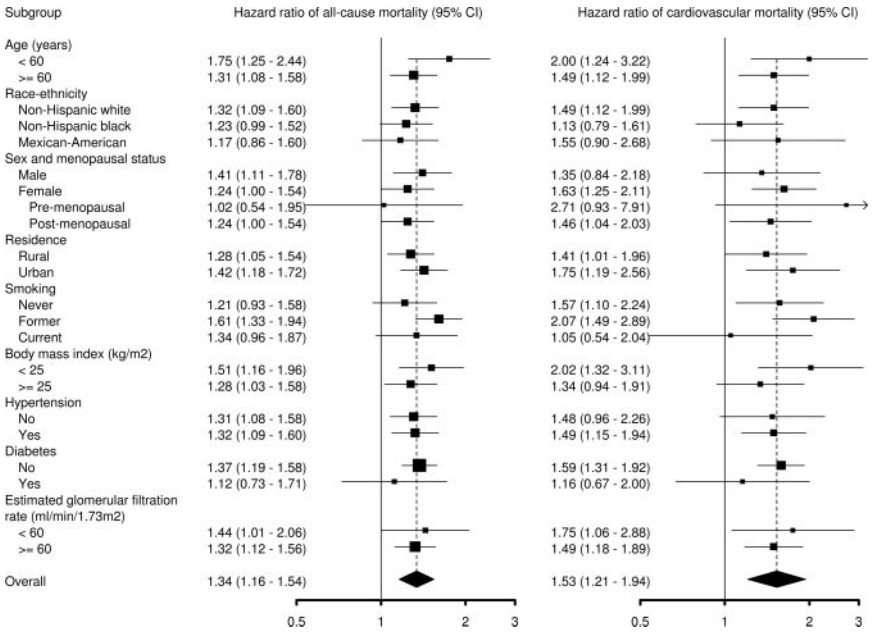

Figure 2. Multivariate adjusted relative hazards of all-cause and cardiovascular mortality. Hazard ratios were calculated for a 3.4-fold increase in blood lead with log–blood lead as a continuous variable. This increase corresponds to the difference between the 80th and 20th percentiles of the blood lead distribution (0.24 μmol/L [4.92 μg/dL] versus 0.07 μmol/L [1.46 μg/dL], respectively).

British Regional Heart Study was also relatively high (mean 0.74 μmol/L [15.3 μg/dL]), and dose–response relationships below 0.48 μmol/L (10 μg/dL) were not reported. Accumulating evidence indicates that blood lead levels <0.48 μmol/L (10 μg/dL) are associated with several health outcomes, including peripheral arterial disease, impaired renal function, and elevated blood pressure.[10–14] The present study adds important data on total and cardiovascular mortality, end points of unquestionable public health relevance, to the list of health outcomes that are associated with blood lead levels below 0.48 μmol/L (10 μg/dL).

The association between lead and cardiovascular disease is biologically plausible. Increases in blood pressure and renal damage have been observed after induction of lead exposure in rodent models.[15,16] However, because these experimental studies have been conducted at doses that produce blood lead levels in rodents >10 times the median reported in NHANES III, the relevance of these studies to the range of blood lead levels reported in the present study is uncertain. In other epidemiological studies, associations between blood lead with increased blood pressure and decreased GFR have been observed at blood lead levels <0.48 μmol/L (10 μg/dL).[2,10,17,18] However, the extent to which blood pressure and renal impairment mediated the effect of lead in the present study is unclear. Although the association between blood lead and cardiovascular disease outcomes persisted after adjustment for estimated GFR, estimated GFR is considered a crude measure of renal function. Studies using more sensitive biomarkers of early kidney damage and renal tubular dysfunction, such as cystatin C, retinal binding protein, and other low-molecular-weight proteins, may be informative in understanding the mechanism underlying lead-associated cardiovascular disease.[15] Weaver and colleagues[19] have reported that hyperfiltration can be measured in workers exposed to lead at substantially lower levels than those associated with decrements in estimated GFR. Alterations in signal transduction that involve renal pathways (eg, angiotensin and vasopressin) have been reported in animal models and also need to be investigated. Additionally, lead may increase cardiovascular risk via inhibition of endothelial nitric oxide synthase, although the evidence for this mechanism in humans is mixed.[20–22] Other biologically plausible mechanisms by which lead may increase cardiovascular risk include effects on neuromuscular control of vascular tone and/or central nervous system neurohumoral regulation of vascular function, sodium transport abnormalities, and alterations in cytosolic calcium regulation.[23–26] Additional research is needed to establish the mechanism responsible for lead-related mortality below 0.48 μmol/L(10 μg/dL).

The findings from the present study need to be considered within the context of its limitations. Perhaps the most important limitation was the reliance on a single blood lead measurement to assess exposure. Blood lead, with a half-life of ≈30 days, reflects primarily recent external exposures, although it is also influenced by long-term exposures through efflux of lead from bone stores. Both blood lead, which reflects recent exposure, and bone lead, which reflects cumulative exposure, have been associated with blood pressure increases.[27–29] Thus, it is unclear whether the adverse health effects of lead observed here were associated with current or cumulative exposures. In addition, because of declining lead levels in the decades before lead ascertainment in the present analysis, it is unclear whether the observed increased risk in mortality was due to lead exposure at baseline or lead mobilization from the skeleton. In the latter scenario, blood lead levels in 1988 to 1994 may reflect prior exposure. The results of the present study emphasize the need for cumulative lead measurements, such as bone lead, which would provide a more accurate characterization of the relationship between long-term lead exposure and mortality. Furthermore, blood lead levels decreased in the US population during the follow-up period, from a geometric mean of 0.13 μmol/L (2.72 μg/dL) in 1988 to 1994 to 0.08 μmol/L (1.64 μg/dL) in 1999 to 2002. Because of regression dilution bias, the

decrease in blood lead observed at the population level implies that the results of the present study are conservative and that the lead–mortality relationship may be stronger than reported. An additional limitation was the lack of active follow-up of NHANES III study participants. Therefore, incident nonfatal events were not obtained. As a consequence, the present findings cannot be generalized to nonfatal events. Although the reliability of mortality follow-up through the National Death Index is very high (98.5%), this method is based on death certificates, which may contain inaccurate information on causes of death. Follow-up was censored at age 90 years because mortality was very high after this age, and few participants contributed person-time experience in this age category. However, all analyses were repeated without censoring of participants aged ≥90 years, and the results were remarkably similar. Finally, we cannot rule out residual confounding by sociodemographic determinants of lead exposure. We note, however, that the association of lead with all-cause and cardiovascular mortality persisted after adjustment for race-ethnicity, household income, education, and urban residence. In addition, the lead–mortality association was observed for cardiovascular diseases but not for cancer, which makes it less likely that residual confounding by sociodemographic factors could explain our findings.

Despite these limitations, the present study maintains several strengths. NHANES III data were collected by a rigorous study protocol with extensive quality control procedures and with technicians trained and certified in all data collection procedures. The results are representative of the US noninstitutionalized civilian population. To the best of our knowledge, the sample size of the NHANES III Mortality Study makes it the largest prospective cohort study of lead exposure and mortality conducted to date. The large sample size permitted the investigation of the effect of blood lead in important subgroups, after adjustment for important confounders and potential intermediates, and after exclusion of patients with a history of cardiovascular disease and cancer at baseline.

Most importantly, the present study for the first time permitted the investigation of the association between blood lead levels below 0.48 μmol/L (10 μg/dL) and mortality end points. The association detected provides new evidence of the adverse impact of lead at levels that are still considered by many to be acceptable, particularly for adult exposures.[30] This association may be surprising to some, but it is important to place it in an historical context. Current population blood lead levels are estimated to be substantially higher than blood lead levels in preindustrialized human societies.[31] Although a 10-fold decline in blood lead levels has occurred in the United States in recent decades, current levels remain orders of magnitude higher than in preindustrialized times. In the present study data, the association of blood lead with cardiovascular mortality was evident at levels as low as 0.10 μmol/L (2 μg/dL). Because 38% of US adults had lead levels >0.10 μmol/L (2 μg/dL) in NHANES 1999 to 2002, the public health implications of these findings are substantial. The health effects of current lead levels on adult populations, however, are not viewed as a pressing public health concern. The present study, in conjunction with previous data, indicates that this perception may be erroneous and that acceptable blood lead levels in adults need further investigation. The results of the present study call for the inclusion of lead exposure at levels <0.48 μmol/L (10 μg/dL) among adult-related cardiovascular risk factors.

Sources of Funding

This study was conducted through funding from National Institutes of Health grant No. P20 RR17659-01 from the COBRE Program of the National Center for Research Resources.

Disclosures

None.

References

1. Lustberg M, Silbergeld E. Blood lead levels and mortality. *Arch Intern Med*. 2002;162:2443–2449.
2. Muntner P, Menke A, DeSalvo KB, Rabito FA, Batuman V. Continued decline in blood lead levels among adults in the United States: the National Health and Nutrition Examination Surveys. *Arch Intern Med*. 2005;165:2155–2161.
3. Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, Matte TD. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). *JAMA*. 1994;272:284–291.
4. National Center for Health Statistics. *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–1994*. Washington, DC: US Dept of Health & Human Services; 1994:1. Publication No. 94-1308.
5. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, Levey AS. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis*. 2002;39:920–929.
6. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130:461–470.
7. Gunter EW, Lewis BG, Koncikowski SM. *Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994*. Atlanta, Ga: US Dept of Health & Human Services; 1996:VII-H-1–VII-H-21.
8. Sassa S, Granick JL, Granick S, Kappas A, Levere RD. Studies in lead poisoning, I: microanalysis of erythrocyte protoporphyrin levels by spectrophotometry in the detection of chronic lead intoxication in the subclinical range. *Biochem Med*. 1973;8:135–148.
9. Pocock SJ, Shaper AG, Ashby D, Delves HT, Clayton BE. The relationship between blood lead, blood pressure, stroke, and heart attacks in middle-aged British men. *Environ Health Perspect*. 1988;78:23–30.
10. Muntner P, He J, Vupputuri S, Coresh J, Batuman V. Blood lead and chronic kidney disease in the general United States population: results from NHANES III. *Kidney Int*. 2003;63:1044–1050.
11. Navas-Acien A, Selvin E, Sharrett AR, Calderon-Aranda E, Silbergeld E, Guallar E. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. *Circulation*. 2004;109:3196–3201.
12. Nordberg M, Winblad B, Fratiglioni L, Basun H. Lead concentrations in elderly urban people related to blood pressure and mental performance: results from a population-based study. *Am J Ind Med*. 2000;38:290–294.
13. Telisman S, Jurasovic J, Pizent A, Cvitkovic P. Blood pressure in relation to biomarkers of lead, cadmium, copper, zinc, and selenium in men without occupational exposure to metals. *Environ Res*. 2001;87:57–68.
14. Vupputuri S, He J, Muntner P, Bazzano LA, Whelton PK, Batuman V. Blood lead level is associated with elevated blood pressure in blacks. *Hypertension*. 2003;41:463–468.
15. Staessen JA, Lauwerys RR, Bulpitt CJ, Fagard R, Linjen P, Roels H, Thijs L, Amery A. Is a positive association between lead exposure and blood pressure supported by animal experiments? *Curr Opin Nephrol Hypertens*. 1994;3:257–263.
16. Victery W. Evidence for effects of chronic lead exposure on blood pressure in experimental animals: an overview. *Environ Health Perspect*. 1988;78:71–76.

17. Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: the Normative Aging Study. *Am J Epidemiol*. 2001;153:164–171.
18. Payton M, Hu H, Sparrow D, Weiss ST. Low-level lead exposure and renal function in the Normative Aging Study. *Am J Epidemiol*. 1994;140:821–829.
19. Weaver VM, Lee BK, Todd AC, Jaar BG, Ahn KD, Wen J, Shi W, Parsons PJ, Schwartz BS. Associations of patella lead and other lead biomarkers with renal function in lead workers. *J Occup Environ Med*. 2005;47:235–243.
20. Gonick HC, Ding Y, Bondy SC, Ni Z, Vaziri ND. Lead-induced hypertension: interplay of nitric oxide and reactive oxygen species. *Hypertension*. 1997;30:1487–1492.
21. Gonick HC. Lead, renal disease and hypertension. *Am J Kidney Dis*. 2002;40:202–204.
22. Lustberg ME, Schwartz BS, Lee BK, Todd AC, Silbergeld EK. The G(894)-T(894) polymorphism in the gene for endothelial nitric oxide synthase and blood pressure in lead-exposed workers from Korea. *J Occup Environ Med*. 2004;46:584–590.
23. Ni Z, Hou S, Barton CH, Vaziri ND. Lead exposure raises superoxide and hydrogen peroxide in human endothelial and vascular smooth muscle cells. *Kidney Int*. 2004;66:2329–2336.
24. Chang HR, Tsao DA, Yu HS, Ho CK. Beta-adrenergic receptor density and adenylate cyclase activity in lead-exposed rat brain after cessation of lead exposure. *Arch Toxicol*. 2005;79:1–6.
25. Boscolo P, Carmignani M, Sacchettoni-Logroscino G, Rannelletti FO, Artese L, Preziosi P. Ultrastructure of the testis in rats with blood hypertension induced by long-term lead exposure. *Toxicol Lett*. 1988;41:129–137.
26. Batuman V. Lead nephropathy, gout, and hypertension. *Am J Med Sci*. 1993;305:241–247.
27. Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A. The relationship of bone and blood lead to hypertension: the Normative Aging Study. *JAMA*. 1996;275:1171–1176.
28. Schwartz J. Lead, blood pressure, and cardiovascular disease in men. *Arch Environ Health*. 1995;50:31–37.
29. Lee BK, Lee GS, Stewart WF, Ahn KD, Simon D, Kelsey KT, Todd AC, Schwartz BS. Associations of blood pressure and hypertension with lead dose measures and polymorphisms in the vitamin D receptor and delta-aminolevulinic acid dehydratase genes. *Environ Health Perspect*. 2001;109:383–389.
30. United Nations Environment Programme, International Labour Organisation, and World Health Organization. International Program on Chemical Safety (IPCS): Inorganic Lead [IPCS INCHEM Web site]. Available at: http://www.inchem.org/documents/ehc/ehc/ehc165.htm. 1995. Geneva, Switzerland: World Health Organization; 1995. Accessed February 21, 2006.
31. Flegal AR, Smith DR. Lead levels in preindustrial humans. *N Engl J Med*. 1992;326:1293–1294.

CLINICAL PERSPECTIVE

We studied the association between blood lead levels and mortality over 12 years of follow-up in a representative sample of the US population. We found that blood lead levels as low as 0.10 μmol/L (2 μg/dL), currently considered safe, were associated with an increased risk of overall mortality and an increased risk of mortality due to coronary heart disease and stroke. Blood lead levels were not associated with cancer mortality. Because 38% of US adults had lead levels >0.10 μmol/L (2 μg/dL) in 1999 to 2002, the public health implications of these findings are substantial. The health effects of current lead levels on adult populations, however, are not viewed as a pressing public health concern. The present study, in conjunction with previous data, indicates that this perception may not be justified and that the current regulations for acceptable blood lead levels in adults are now outdated and may need to be revised. Because of the limited ability the present study had to evaluate the risks of lead exposure associated with blood lead levels below 0.10 μmol/L (2 μg/dL), there is a need for future research to identify the level of lead exposure that is no longer associated with adverse health outcomes. Although markedly reduced, current blood lead levels may not be low enough; practicable and cost-effective methods for reducing lead exposure in the general US population are needed. ?? ?? ?? ??