

Low-Level Environmental Exposure to Lead Unmasked as Silent Killer

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Since the dawn of human civilization, lead has been a ubiquitous environmental pollutant.¹ In 370 BC, Hippocrates described colic in a lead worker.² The industrial application of lead continues to the present day. Lead is a toxic metal that, during a lifetime, accumulates in the human body.¹ Recent evidence^{3–6} suggests that lead affects human health at levels of exposure that, until now, were considered safe. The underlying premise is that a dose-related continuum of toxicity exists. Asymptomatic health effects may occur at even a very low dose and may evolve into clinically overt adverse effects if the exposure persists during a person's lifetime or becomes more intense. The report published by Menke et al⁷ in this issue of *Circulation* breaks new ground by extending the dose–effect relation to considerably lower blood lead concentrations than reported in previous studies.^{3–6}

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Menke et al⁷ analyzed the database of the Third National Health and Nutrition Examination Survey (NHANES III) to investigate the relation between total and cause-specific mortality and blood lead in a representative sample of the US population. All 13 946 participants (≥ 17 years of age) included in the analysis had a blood lead concentration < 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$). (To convert micromoles per liter of lead into micrograms per deciliter, multiply by 20.712.) Follow-up lasted until December 31, 2000. With adjustments applied for confounders, subjects in the highest third of the blood lead distribution (≥ 0.17 $\mu\text{mol/L}$), as compared with those in the lowest third (< 0.09 $\mu\text{mol/L}$), experienced a significantly higher risk of death. Estimates of the excess risk amounted to 25% and 55% for total and cardiovascular mortality, respectively, and 89% and 151% for myocardial infarction and stroke.⁷ The blood lead concentration did not predict mortality from cancer. These risk estimates withstood adjustment for confounders, including race-ethnicity, sex, age, body

mass index, current or former smoking, alcohol intake, diabetes, C-reactive protein, total cholesterol, physical activity, low income, high education, urban residence, and postmenopausal status. Sensitivity analyses of total mortality stratified for race, sex, age, body mass index, smoking, hypertension, diabetes, calculated glomerular filtration rate, and urban versus rural residence also produced consistent results. Spline regression models additionally demonstrated that the all-cause and cardiovascular mortality started to rise at blood lead levels as low as 0.10 $\mu\text{mol/L}$.⁷

Two previous population studies^{8,9} documented an association between total mortality and blood lead, albeit at higher blood lead concentrations than in the Menke et al⁷ report. Among 1052 inhabitants recruited in 1976 at 40 years of age in Copenhagen County (Denmark), the blood lead concentration was 0.46 $\mu\text{mol/L}$ in women and 0.66 $\mu\text{mol/L}$ in men.⁸ Blood lead fell by $\approx 30\%$ over the first 5 years of follow-up. Over 14 years, 46 deaths occurred, and the incidence of fatal and nonfatal events totaled 54 for cardiovascular disorders and 40 for coronary heart disease. With adjustments applied for sex, serum cholesterol, smoking, and alcohol intake, the risk associated with blood lead at baseline was of borderline significance ($P=0.03$) for total mortality but it was not significant for fatal and nonfatal cardiovascular disease or coronary complications. Further adjustment for alcohol intake weakened the hazard ratio for total mortality to a nonsignificant level ($P=0.12$).⁸ The NHANES II investigators recruited participants (age, 30 to 74 years) from 1976 until 1980. Of the 4292 subjects who had their blood lead measured at baseline, 102 were excluded from analysis because their lead concentration exceeded the contemporary standard of the Occupational Safety and Health Administration (1.45 $\mu\text{mol/L}$). Of the remaining 4190 subjects, 929 had died by December 31, 1992.⁹ Compared with the reference group with a blood lead concentration < 0.48 $\mu\text{mol/L}$, the multivariate-adjusted hazard ratios were significant for total (1.46), cardiovascular (1.39), and cancer (1.68) mortality in the subgroup with a blood lead concentration of ≥ 0.97 $\mu\text{mol/L}$ but not in the subgroup with intermediate levels (hazard ratios, 1.17, 1.10, and 1.46, respectively).⁹ The report from Lustberg and Silbergeld⁹ did not provide any rationale for the cutoff thresholds to categorize the NHANES II participants or information on the number of subjects or deaths per category. In 2004, the same group reported a cross-sectional analysis of 2125 participants who were 40 years of age in the 1999 to 2000 NHANES survey.⁵ The mean blood lead concentration was 0.10 $\mu\text{mol/L}$. Peripheral arterial disease was defined as an ankle brachial index < 0.9 in at least one leg. With cumulative adjustment for demographics and cardiovascular risk factors, the odds ratios in quartiles 2 to 4 of the blood

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lead distribution compared with the lowest quartile were 1.63 (95% CI, 0.51 to 5.15), 1.92 (95% CI, 0.62 to 9.47), and 2.88 (95% CI, 0.87 to 9.47), respectively.⁵ Although the CIs of the odds ratios encompassed unity, the probability value for trend was 0.02. Navas-Acien et al⁵ concluded that peripheral arterial disease was associated with blood lead levels well below current safety standards. In 428 participants in the Flemish Study on Environment, Genes, and Health Outcomes,¹⁰ we replicated the observations of Navas-Acien et al, albeit it at a mean lead concentration of 0.43 $\mu\text{mol/L}$.

In the Menke et al⁷ study, the association of total and cardiovascular mortality with blood lead persisted after adjustment for hypertension, an estimated glomerular filtration rate $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, and C-reactive protein. These observations suggest, but by no means prove, that mechanisms other than hypertension, impaired renal function, and inflammation might underlie the observed associations. Indeed, with the exception of cases of frank lead intoxication,¹ the relation between hypertension and exposure to lead, remains controversial.

The suspicion that environmental lead exposure might play a role in the pathogenesis of hypertension arose mainly after publication of NHANES II reports^{11,12} describing a direct relation between blood pressure and blood lead, which was particularly strong in white middle-aged men. However, other researchers found later that the positive correlation in 40- to 59-year-old men did not characterize the other sex and age strata and questioned the quality of the blood pressure measurements.^{13,14} In a meta-analysis of 31 studies,¹⁵ we found that a doubling of the blood lead concentration entailed increases in blood pressure averaging 1.0 mm Hg (0.5 to 1.4 mm Hg) systolic and 0.6 mm Hg (0.4 to 0.8 mm Hg) diastolic. Furthermore, in 1985 to 1989, we randomly selected 728 subjects (≥ 20 years of age) from a Belgian population.¹⁶ Over 5.2 years of follow-up (median), the mean blood lead concentration, initially 0.42 $\mu\text{mol/L}$, dropped by 32%. In this prospective study,¹⁶ we did not notice any consistent relation between the changes over time in blood pressure on conventional sphygmomanometric measurement and those in blood lead. Moreover, the blood lead concentration at baseline did not predict the 24-hour ambulatory blood pressure at follow-up. Ambulatory blood pressure recordings have high reproducibility, are not subject to digit preference or observer bias, and avoid the transient rise in a patient's blood pressure in response to a medical environment, the so-called white-coat effect. Cheng et al¹⁷ reported on 519 men enrolled in the Normative Aging Study who were free of hypertension at baseline. With adjustments applied for the linear and squared terms of age, body mass index, family history of hypertension, alcohol use, and calcium intake, the standardized hazard ratios for the risk of hypertension over the 5.5-year follow-up were 1.37 (95% CI, 0.02 to 2.73) for tibia lead, a biomarker for long-term exposure, but only -0.13 (95% CI, -1.35 to 1.09) for blood lead. Unfortunately, the Cheng et al¹⁷ analysis was not adjusted for baseline blood pressure or for the percentage change in body weight, both of which are important determinants of the incidence of hypertension.¹⁸ Finally, our own analysis of the NHANES III database¹⁹ demonstrated only a weak multivar-

iate-adjusted association between blood pressure and blood lead in blacks but not in whites.

The evidence that changes in renal function might represent an intermediate mechanism possibly explaining the association between mortality and environmental lead exposure might be more plausible than that of hypertension. In 1992, in a cross-sectional population study of 1016 women and 965 men (≥ 20 years of age) with mean blood concentrations of 0.36 and 0.55 $\mu\text{mol/L}$, respectively, we observed that a 10-fold increase in blood lead was associated with a 10- to 12-mL/min reduction in the measured creatinine clearance.⁴ More recently, in adolescents with a mean blood lead concentration of 0.09 $\mu\text{mol/L}$, we noticed an independent and positive association of the serum concentration of cystatin-c and the urinary excretion of β_2 -microglobulin with blood lead.³ Serum cystatin-c is a measure of glomerular filtration that, unlike serum creatinine, is independent of sex, age, height, and body composition. β_2 -Microglobulin passes through the glomerular filter but is subsequently completely absorbed by the renal tubules. Our observations,^{3,4} in agreement with other reports,²⁰ suggested that in adolescents environmental lead exposure can affect both glomerular and tubular renal function. Reverse causality is always an issue in observational studies. However, the alternative hypothesis—that slight renal dysfunction, resulting from innate or acquired causes, might reduce the renal excretion of lead and explain the positive association between renal dysfunction and the blood lead concentration—is unlikely. Indeed, Lin et al²¹ reported that high-normal levels of chelatable lead predicted the decline of renal function in patients with chronic renal insufficiency. Moreover, chelation therapy in these patients improved renal function and slowed the progression of renal impairment.²¹ These findings implied that, in line with the findings in intoxicated workers¹ and in environmentally exposed subjects,^{3,4} increased blood lead must be the cause rather than the consequence of renal impairment. In addition to renal dysfunction, several other mechanisms might underlie the toxic effects of lead on the cardiovascular system such as enhanced vascular reactivity to sympathetic stimulation, enhanced oxidative stress, and diminished DNA repair, which might be relevant for rapidly dividing cells in the inflamed arterial wall.

Menke et al⁷ carefully discussed the results of their study within the context of its possible limitations such as residual confounding. Two major limitations and one strong point deserve to be highlighted. First, blood lead has a half-life of ≈ 30 days. Its concentration in the blood primarily reflects recent exposure and can revert to normal when exposure ceases.¹ However, within days to weeks, lead is stored in tissues, particularly bones, which hold $\approx 90\%$ of the body burden. Bone lead has a biological half-life ranging from 7 years to several decades.¹ Bone remodeling, like that which occurs in postmenopausal women, releases lead into the blood, a process described as endogenous contamination. Thus, in the Menke et al report,⁷ the blood lead concentrations might reflect exposure levels before 1988 to 1994, which were considerably higher than at present. Second, the introduction of intensive care units, invasive coronary procedures, and thrombolysis reduced the case-fatality rate of cardiovas-

cular complications. Not accounting for nonfatal events, as in the Menke et al report,⁷ limits the generalizability of the results. On the other hand, in contrast to some previous reports based on an arbitrary classification of subjects according to blood lead,⁹ Menke et al confirmed their categorical results by a continuous analysis relating mortality to blood lead.

In view of the Menke et al⁷ report and our observations in adolescents,³ blood lead concentrations as low as 0.10 $\mu\text{mol/L}$ likely represent a public health hazard. In NHANES 1999 to 2000,⁵ 38% of US adults had a blood lead level above this threshold. This proportion is likely to be higher among the less privileged in industrialized countries and among citizens of developing countries, where environmental regulations are either less stringent, nonexistent, or not applied. In areas with historical contamination of the soil by heavy metals, house dust remains a persistent source of exposure even decades after the cessation of the industrial activity.²² People living on polluted soils remain exposed to lead via fine particulate (PM10) suspended in the air at a level 17 times the normal background value (measuring station OBE01, 576 versus 17 ng/m^3 ; <http://www.vmm.be>, accessed on August 2, 2006). Belgium is no exception, and similar levels of environmental exposure likely persist in the United States and other European countries. Almost 5 years ago, we reported to our government that such exposure levels are intolerable.³ Worldwide, regulators and the industry should no longer remain indifferent but accept their responsibility.

Disclosures

None.

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KEY WORDS: epidemiology ■ mortality ■ hypertension ■ risk factors ■ lead

Blood Lead Below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) and Mortality Among US Adults

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Background—Blood lead levels above 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) 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 $\mu\text{mol/L}$ 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 $\mu\text{mol/L}$ (2.58 $\mu\text{g/dL}$). After multivariate adjustment, the hazard ratios (95% CI) for comparisons of participants in the highest tertile of blood lead (≥ 0.17 $\mu\text{mol/L}$ [≥ 3.62 $\mu\text{g/dL}$]) with those in the lowest tertile (< 0.09 $\mu\text{mol/L}$ [< 1.94 $\mu\text{g/dL}$]) 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 $\mu\text{mol/L}$ (≥ 2 $\mu\text{g/dL}$). 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 $\mu\text{mol/L}$ (40 $\mu\text{g/dL}$) have been associated with increased risks of cardiovascular, cancer, and all-cause mortality in several occupational cohorts. In the general population, Lustberg and Silbergeld¹ also reported significant relationships between blood lead levels above 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) 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 $\mu\text{mol/L}$ (13.1 $\mu\text{g/dL}$) in 1976 to 1980 to 0.08 $\mu\text{mol/L}$ (1.6 $\mu\text{g/dL}$) in 1999 to 2002. Currently, 99% of US adults have blood lead levels below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$).² To the best of our knowledge, the association of

blood lead levels below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) 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 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) 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 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$), and 1494 participants who were missing other

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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 \cdot min⁻¹ \cdot 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 μ mol/L (1.0 μ g/dL). For 8.1% of study participants with lead levels below the detection limit, we imputed a level of 0.03 μ mol/L (0.7 μ g/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 μ mol/L [1.00 μ g/dL], 0.13 μ mol/L [2.67 μ g/dL], and 0.29 μ mol/L [5.98 μ g/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 μ mol/L [4.92 μ g/dL] versus 0.07 μ mol/L [1.46 μ g/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 μ mol/L [2.58 μ g/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 ($<0.09 \mu\text{mol/L}$ or $<1.93 \mu\text{g/dL}$)	Tertile 2 ($0.09\text{--}0.17 \mu\text{mol/L}$ or $1.94\text{--}3.62 \mu\text{g/dL}$)	Tertile 3 ($\geq 0.18 \mu\text{mol/L}$ or $\geq 3.63 \mu\text{g/dL}$)	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 $< 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$, %	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 $P_{\text{trend}} < 0.05$). 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 $> 0.10 \mu\text{mol/L}$ ($2.0 \mu\text{g/dL}$; 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 $> 0.10 \mu\text{mol/L}$ ($2.0 \mu\text{g/dL}$). 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 $1.93 \mu\text{mol/L}$ ($40 \mu\text{g/dL}$) 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 Silbergeld¹ 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 ($<0.09 \mu\text{mol/L}$ or $<1.93 \mu\text{g/dL}$)	Tertile 2 ($0.09\text{--}0.17 \mu\text{mol/L}$ or $1.94\text{--}3.62 \mu\text{g/dL}$)	Tertile 3 ($\geq 0.18 \mu\text{mol/L}$ or $\geq 3.63 \mu\text{g/dL}$)	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.

$>0.48 \mu\text{mol/L}$ ($10 \mu\text{g/dL}$) and all-cause, cardiovascular, and cancer mortality. Blood lead levels in adults at the time of NHANES II (geometric mean $0.63 \mu\text{mol/L}$ [$13.1 \mu\text{g/dL}$]) 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

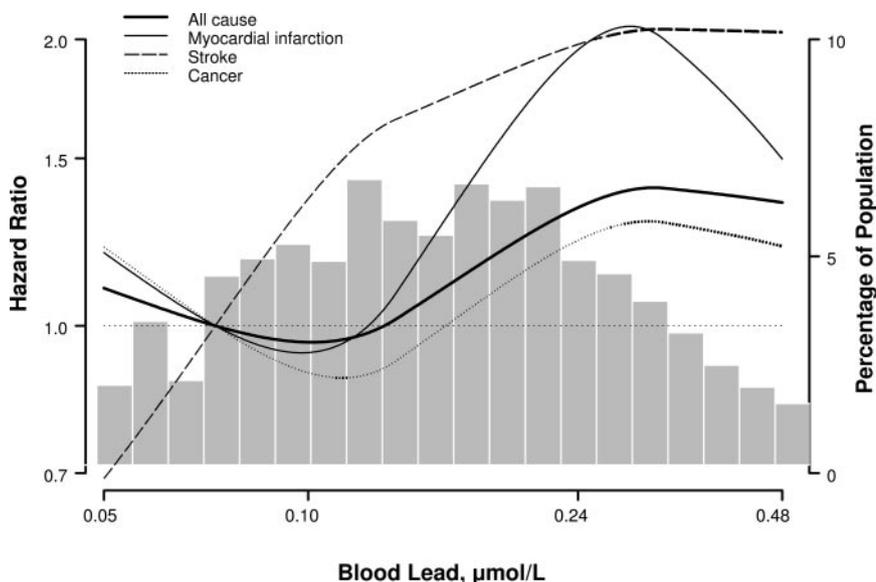


Figure 1. Multivariate adjusted relative hazard (left axis) of mortality associated with blood lead levels between $0.05 \mu\text{mol/L}$ ($1 \mu\text{g/dL}$) and $0.48 \mu\text{mol/L}$ ($10 \mu\text{g/dL}$). Histogram of blood lead levels is superimposed in the background and displayed on the right axis.

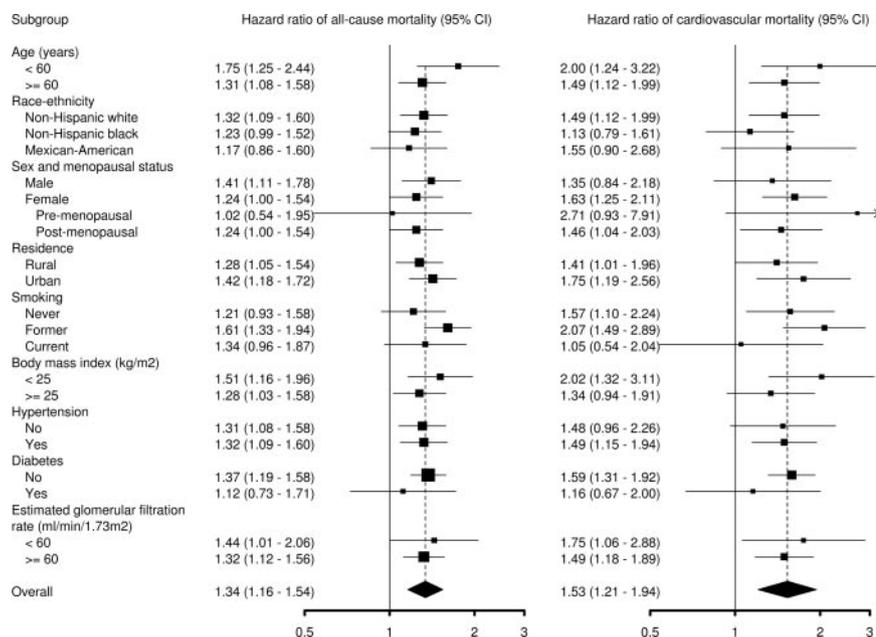


Figure 2. Multivariate adjusted relative hazards of all-cause and cardiovascular mortality. Hazard ratios were calculated for a 3.4-fold increase in blood lead with log–blood lead as a continuous variable. This increase corresponds to the difference between the 80th and 20th percentiles of the blood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

British Regional Heart Study was also relatively high (mean 0.74 $\mu\text{mol/L}$ [15.3 $\mu\text{g/dL}$]), and dose–response relationships below 0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) were not reported. Accumulating evidence indicates that blood lead levels <0.48 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) 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 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$).

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 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$).^{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 colleagues¹⁹ 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 vaso-

pressin) 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 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$).

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 $\mu\text{mol/L}$ (2.72 $\mu\text{g/dL}$) in 1988 to 1994 to 0.08 $\mu\text{mol/L}$ (1.64 $\mu\text{g/dL}$) 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 $0.48 \mu\text{mol/L}$ ($10 \mu\text{g/dL}$) 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 $0.10 \mu\text{mol/L}$ ($2 \mu\text{g/dL}$). Because 38% of US adults had lead levels $>0.10 \mu\text{mol/L}$ ($2 \mu\text{g/dL}$) 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 $<0.48 \mu\text{mol/L}$ ($10 \mu\text{g/dL}$) among adult-related cardiovascular risk factors.

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Disclosures

None.

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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 $\mu\text{mol/L}$ (2 $\mu\text{g/dL}$), 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 $\mu\text{mol/L}$ (2 $\mu\text{g/dL}$) 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 $\mu\text{mol/L}$ (2 $\mu\text{g/dL}$), 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. ?? ?? ?? ??