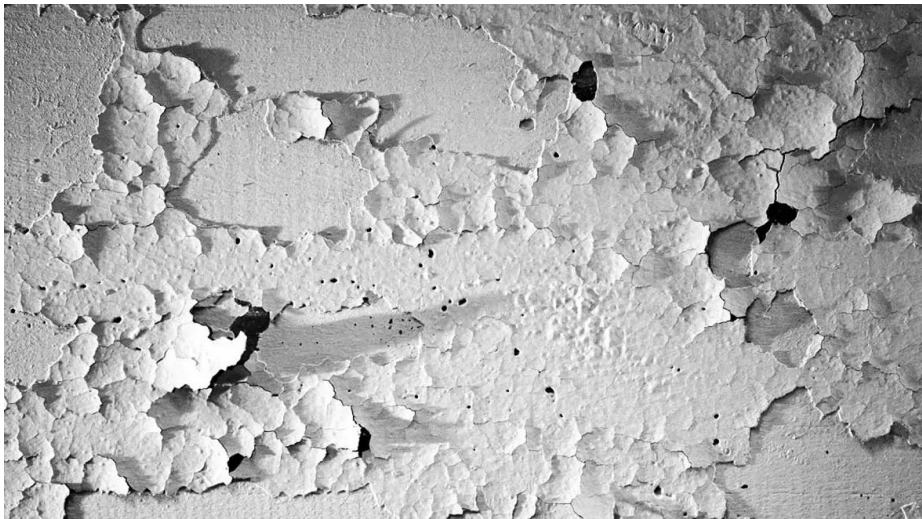


New Study Links Lead Exposure to Heart Disease Deaths

The research suggests that even low-level exposure may be a significant risk factor for heart disease

By Catherine Roberts
March 12, 2018



Lead exposure may contribute to more than 400,000 deaths of adults each year in the U.S., according to an estimate [published today in the journal Lancet Public Health](#).

That number includes 256,000 annual deaths from cardiovascular disease, suggesting that lead exposure may be a significant, overlooked risk factor for this leading cause of death. The estimate was extrapolated from a nationally representative sample of 14,289 adults, whose blood had been tested for lead sometime between 1988 and 1994.

Lead exposure is “ubiquitous, but insidious,” the researchers have written.

People can be exposed to lead through paint, household dust, food, water, and cigarette smoke, as well as through some industrial jobs. Childhood exposure to lead is known to increase the risk for delayed development, behavior problems, IQ deficits, hearing and speech problems, and more, [according to the Centers for Disease Control and Prevention](#).

Lead levels in children were much higher until the 1970s, when lead was removed from gasoline and paint. But while lead exposure is considered a risk factor for heart disease and both the CDC and the Environmental Protection Agency have warned that [lead is unsafe at any level](#), this is the first study to quantify just how severe the toll might be—even at the lowest levels, and even decades after exposure.

The research underscores the danger lead poses [not only to children](#) but also to adults, according to Bruce Lanphear, M.D., M.P.H., a professor of health sciences at Simon Fraser University in British Columbia and the study's lead author. "There's no apparent threshold or safe level [of lead] for deaths from heart disease," he says.

Here's what you need to know about this research and what you can do to [protect yourself now](#) from the dangers of lead.

What the New Research Found

While this new estimate is staggering, the results should be interpreted cautiously, experts say.

One limitation: Lead levels in the blood were measured only once. Lead may be stored in the body for years after initial exposure, but the concentration of lead in blood can change over time. Other potential risk factors, such as diet and smoking habits, were also assessed only once and were not tracked over time. And while the researchers controlled for other risk factors to try to zero in on the effects of lead, they acknowledge that they were not able to account for everything that might contribute to the deaths.

For example, says Eliseo Guallar, M.D., Dr.P.H., a professor of epidemiology and medicine at Johns Hopkins University who wasn't involved with the new study, "lead exposure might be a marker also of disadvantaged socioeconomic status," which may be linked to risky behaviors or conditions (such as higher rates of air pollution) that the new study couldn't adjust for.

Average blood lead levels are also probably lower today for the general population than they were in the late 1980s and early 1990s, when the initial data for the new study was collected, says Ana Navas-Acien, M.D., Ph.D., professor of environmental health sciences at Columbia University in New York City who also wasn't involved with the new study. So while the study included people who died as recently as 2011, the number of deaths that can be linked to lead may be smaller today. "We'd expect somewhat less risk for the next generation," Lanphear says.

Still, both Navas-Acien and Guallar say that the new study is convincing overall and highlights the often-ignored impact that lead exposure can have on heart health. The pair collaborated on a study released last year that evaluated the same data that Lanphear's team used and found that approximately a third of the decline in heart disease deaths from the early 1990s to the early 2000s could be explained by reduced exposures to lead and the heavy metal cadmium.

How to Protect Yourself From Lead

Lead is no longer allowed in gasoline and paint in the U.S. and many other countries. But the substance can still lurk in unexpected places.

Here, what you can do to reduce your exposure to lead.

Check for lead paint. If your home was built before 1978, it's likely that at least some lead paint was

used in it. As the paint degrades, chips, or crumbles from normal use or renovation, it gets into household dust, which can find its way into your system when you breathe or accidentally inhale it. You can test for lead in paint using a kit available at your local hardware store. For detailed instructions on how to get the test right, see our guide [here](#).

If you do find lead paint, don't sand, scrape, or demolish the surface on your own. You'll first need to hire an EPA-certified lead-abatement professional. Or you can paint over the contaminated area yourself, provided you don't disturb the leaded layer.

Beware of lead pipes. If your home was built before 1986, its water pipes could contain lead and you should use only cold water from the tap for drinking and cooking. According to the CDC, hot water is more likely to contain lead. And you may want to have the water in your home tested for lead. (Find a certified lab [here](#).)

Have your children tested. The CDC recommends that children at high risk for lead exposure receive a blood test for the toxin at six months, and at one year for children at low risk. A number of factors can affect kids' risk—including living in or regularly visiting a home built before 1978 that has chipped or peeling paint or that is being (or was recently) renovated. Your doctor can help you figure out your children's level of risk, and when they should be tested.

Pay attention to recalls and other news about lead. "Studies show that lead exposure from consumer goods is not insignificant," says Tunde Akinleye, a test program leader in Consumer Reports' Food Safety Division. The toxin is sometimes discovered in common products such as lipstick, toys, and more. Sometimes these products will be recalled; other times, scientists test items for lead and publicize their findings. Akinleye recommends that consumers pay attention to these reports and look for alternatives to products found to contain the highest amounts of lead.

For example, a recent analysis by the Clean Label Project found lead and other heavy metals in protein shakes and powders, and reported which brands had the highest and lowest levels of toxins. Consumer Reports has tested for lead, arsenic, and cadmium in juice and rice products, and continues to regularly test consumer products for lead.

Low-level lead exposure and mortality in US adults: a population-based cohort study

Bruce P Lanphear, Stephen Rauch, Peggy Auinger, Ryan W Allen, Richard W Hornung



Summary

Background Lead exposure is a risk factor for cardiovascular disease mortality, but the number of deaths in the USA attributable to lead exposure is poorly defined. We aimed to quantify the relative contribution of environmental lead exposure to all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality.

Methods Our study population comprised a nationally representative sample of adults aged 20 years or older who were enrolled in the Third National Health and Nutrition Examination Survey (NHANES-III) between 1988 and 1994 and followed up to Dec 31, 2011. Participants had completed a medical examination and home interview and had results for concentrations of lead in blood, cadmium in urine, and other relevant covariates. Individuals were linked with the National Death Index. This study presents extended follow-up of an earlier analysis.

Findings We included 14 289 adults in our study. The geometric mean concentration of lead in blood was 2.71 µg/dL (geometric SE 1.31). 3632 (20%) participants had a concentration of lead in blood of at least 5 µg/dL (≥ 0.24 µmol/L). During median follow-up of 19.3 years (IQR 17.6–21.0), 4422 people died, 1801 (38%) from cardiovascular disease and 988 (22%) from ischaemic heart disease. An increase in the concentration of lead in blood from 1.0 µg/dL to 6.7 µg/dL (0.048 µmol/L to 0.324 µmol/L), which represents the tenth to 90th percentiles, was associated with all-cause mortality (hazard ratio 1.37, 95% CI 1.17–1.60), cardiovascular disease mortality (1.70, 1.30–2.22), and ischaemic heart disease mortality (2.08, 1.52–2.85). The population attributable fraction of the concentration of lead in blood for all-cause mortality was 18.0% (95% CI 10.9–26.1), which is equivalent to 412 000 deaths annually. Respective fractions were 28.7% (15.5–39.5) for cardiovascular disease mortality and 37.4% (23.4–48.6) for ischaemic heart disease mortality, which correspond to 256 000 deaths a year from cardiovascular disease and 185 000 deaths a year from ischaemic heart disease.

Interpretation Low-level environmental lead exposure is an important, but largely overlooked, risk factor for cardiovascular disease mortality in the USA. A comprehensive strategy to prevent deaths from cardiovascular disease should include efforts to reduce lead exposure.

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Introduction

Deaths from cardiovascular disease have declined strikingly in the USA over the past 50 years, but this disease is still the leading cause of death.¹ In 2013, cardiovascular disease accounted for more than 800 000 deaths in the USA (about one in every three deaths), with total costs exceeding US\$300 billion annually.¹ Cardiovascular disease mortality is usually attributed to tobacco use, hypertension, diabetes, and lack of physical activity.² Environmental lead exposure is an established risk factor for hypertension and a possible risk factor for cardiovascular disease mortality,^{3,4} but its contribution to deaths in the USA is poorly defined.

Lead is one of many recognised risk factors for cardiovascular disease. In experimental studies,^{3,4} chronic exposure to lead caused hypertension and enhanced the development of atherosclerosis by inactivating nitric oxide, increasing formation of hydrogen peroxide, inhibiting endothelial repair, impairing angiogenesis, and promoting thrombosis. In human beings, higher concentrations of lead in blood have been associated

with hypertension, electrocardiographic abnormalities, peripheral arterial disease, left-ventricular hypertrophy, and cardiovascular disease mortality.^{4–13} The concentration of lead in blood was associated with cardiovascular mortality in most, but not all, prospective cohort studies.^{6–13} Previous studies of cardiovascular disease mortality in lead-exposed populations have been criticised because they did not account for other risk factors associated with cardiovascular disease mortality, such as cadmium.^{4,14} No studies have estimated the number of deaths in the USA attributable to lead exposure using a nationally representative cohort, and it is unclear whether concentrations of lead in blood lower than 5 µg/dL (< 0.24 µmol/L), which is the current action level for adults in the USA, are associated with cardiovascular mortality.

The aim of this study was to extend the duration of follow-up of a previously published analysis⁷ and quantify the relative contribution of environmental lead exposure to all-cause mortality and cardiovascular disease mortality using data from the Third National Health and Nutrition

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Faculty of Health Sciences,
Simon Fraser University,
Vancouver, BC, Canada

(Prof B P Lanphear MD,

R W Allen PhD); School of Public

Health, University of California

at Berkeley, Berkeley, CA, USA

(S Rauch MPH); University of

Rochester School of Medicine

and Dentistry, Rochester, NY,

USA (P Auinger MS); and

Cincinnati Children's Hospital

Medical Center, University of

Cincinnati School of Medicine,

Cincinnati, OH, USA

(Prof R W Hornung DrPH)

Correspondence to:

Prof Bruce P Lanphear, Faculty of

Health Sciences, Simon Fraser

University, Vancouver,

BC V6H 3V4, Canada

blanphear@sfu.ca

Research in context

Evidence before this study

We searched PubMed between 1980 and Oct 1, 2017, with terms including “mortality”, “blood lead concentration”, “cardiovascular mortality”, and “population attributable risk”. We also searched citations of all identified studies. We restricted our search to English language publications. We included human studies. Many studies have linked concentrations of lead in blood with hypertension and mortality from cardiovascular disease. The number of deaths in the USA attributable to lead exposure has not been estimated using a nationally representative cohort, and it is unclear if concentrations of lead in blood lower than 5 µg/dL (<0.24 µmol/L) are associated with all-cause mortality or cardiovascular disease mortality.

Added value of this study

Our study is, to our knowledge, the first to estimate in a nationally representative sample the contribution of

concentrations of lead in blood to the number of deaths from all causes and from cardiovascular disease. Although we cannot exclude residual confounding, we estimate that about 400 000 deaths are attributable to lead exposure every year in the USA, of which 250 000 are from cardiovascular disease. Concentrations of lead in blood lower than 5 µg/dL (<0.24 µmol/L) are an important, but largely ignored, risk factor for death in the USA, particularly from cardiovascular disease.

Implications of all the available evidence

Quantifying the contribution of environmental lead exposure to cardiovascular disease mortality is essential to understand trends in mortality and develop comprehensive strategies to prevent cardiovascular disease.

Examination Survey (NHANES-III), a prospective, representative cohort of the US population enrolled from 1988 to 1994 and followed up to Dec 31, 2011.

Methods

Study population

NHANES-III is a multistage stratified survey designed to provide a detailed examination of the health and nutritional status of a nationally representative sample of non-institutionalised individuals in the USA. Consistent with an earlier analysis of this cohort,⁷ we included individuals who were aged 20 years or older at baseline. The protocols for NHANES-III were approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention Institutional Review Board. All participants gave informed consent.

Procedures

Baseline data in NHANES-III were gathered between 1988 and 1994, when individuals participated in a household interview and a medical examination, during which they provided blood and urine samples. Demographic information—including sex, age, ethnic origin, household income, education, residence, smoking status, and social support—was obtained during the household interview. Information on body-mass index (BMI), physical activity, blood pressure, diet, alcohol consumption, medical history, and prescription drug use was obtained during the medical examination.

Amounts of lead in blood, cadmium and creatinine in urine, cotinine and cholesterol in serum, and glycated haemoglobin (HbA_{1c}) were measured from blood and urine samples gathered during the medical examination. Laboratory methods for the processing of blood and urine samples are described in detail elsewhere.¹⁵ Quantification of lead in whole blood samples, which

entailed extensive quality control, was done using graphite furnace atomic absorption spectrophotometry.¹⁶ The detection limit for lead in blood was 1.0 µg/dL (0.048 µmol/L). For study participants who had concentrations of lead in blood below the level of detection, we imputed an amount of 0.7 µg/dL (0.034 µmol/L), which is the level of detection divided by the square root of 2.¹⁷

A full description of mortality linkage methods is available from the National Center for Health Statistics (NCHS).¹⁸ Briefly, NCHS staff linked participants in NHANES-III to underlying cause of death in the National Death Index with a series of identifiers—eg, social security number and date of birth—using probabilistic matching criteria. Individuals were followed up to Dec 31, 2011; if a match was not made with the National Death Index, that person was assumed to be alive as of that date. In a validation study using mortality-linked data from the first NHANES study (NHANES-I; 1971–75), 96% of deceased participants and 99% of those still alive were classified correctly.¹⁹ The underlying cause of death was obtained using codes from the International Classification of Diseases ninth version (ICD-9; 1988–98) or tenth version (ICD-10; 1999–2006). We identified deaths from all causes, cardiovascular disease (ICD-9 390–459; ICD-10 I00–I99) and ischaemic heart disease (ICD-9 410–414; ICD-10 I20–I25; appendix p 1).

Statistical analysis

We have weighted results (percentiles, means, and point estimates) to account for the complex survey design of NHANES-III, and these data are representative of the US Census civilian non-institutionalised population. We calculated hazard ratios (HRs) for continuous concentrations of lead in blood, using Cox proportional hazards models. Every participant's survival—as defined by the

See Online for appendix

NHANES-III protocol—was the time between the medical examination and the date of death, the participant's 90th birthday, or Dec 31, 2011, whichever came first.¹⁸

We assessed concentrations of lead in blood both as a continuous variable and categorically with tertiles. We fitted five-knot restricted cubic splines to visualise the shape of the dose-response relation of concentrations of lead in blood for all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality, and to investigate whether the relations should be judged linear or log-linear.

We weighted demographic and environmental variables to approximate distributions in the USA by using the provided sample weights to account for oversampling of young children, older people, black people, and individuals of Mexican-American ethnic origin in the NHANES-III survey. We adjusted for variables recognised widely as potential confounders for cardiovascular disease mortality.^{2–10} We adjusted all primary models for age (continuous and age-squared), sex, household income (<US\$20 000 or ≥\$20 000 per year), ethnic origin (white, black, Mexican-American), BMI (derived from participants' height and weight measurements and categorised as normal [$<25.0 \text{ kg/m}^2$], overweight [$25.0\text{--}29.9 \text{ kg/m}^2$], or obese [$\geq 30.0 \text{ kg/m}^2$]), smoking status (self-reported [never, current, and former] or amounts of cotinine in serum [$\geq 10 \text{ ng/mL}$]), alcohol consumption (four or fewer drinks per month or more than four drinks per month), physical activity (categorised according to frequency of activity in the previous month [none, 1–14 times, or ≥ 15 times]), and amount of cadmium in urine (standardised by amount of creatinine in urine and categorised in tertiles). Blood pressure was measured three times during the NHANES-III household interview and three times during the medical examination. We excluded the first reading and used the average of all remaining blood pressure measurements to classify every participant's hypertension status (defined as systolic blood pressure $\geq 140 \text{ mm Hg}$ or diastolic blood pressure $\geq 90 \text{ mm Hg}$). The Healthy Eating Index, which was derived from food frequency questionnaires and scored on a scale from 1 to 100, was categorised in tertiles.²⁰ Finally, we included HbA_{1c} and amount of cholesterol in serum as continuous measures.

We calculated population attributable fractions for continuous concentrations of lead in blood using previously described methods²¹ to estimate the proportional reduction in mortality that would occur if recorded amounts of lead in blood in the entire US population aged 20 years and older were reduced to $1.0 \text{ }\mu\text{g/dL}$ ($0.048 \text{ }\mu\text{mol/L}$). Absolute numbers of deaths were based on the average annual number of deaths from all causes, cardiovascular disease, and ischaemic heart disease from 1988 to 2011.^{22,23} The standard method for calculating the population attributable fraction is a simple comparison of the relative risk in the exposed population weighted by the proportion exposed with the relative risk in the unexposed

population weighted by the proportion unexposed. To utilise individual measures of lead in blood and their associated HR estimates, we calculated the population attributable fraction or population impact factor using the integral of the HR estimates weighted by the log-normal population distribution of measured concentrations of lead in blood over the total range ($0.70\text{--}56.0 \text{ }\mu\text{g/dL}$ [$0.034\text{--}2.70 \text{ }\mu\text{mol/L}$]) for all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality, as described previously.¹⁹ We calculated CIs for population

	Total	Concentration of lead in blood (tertiles)			p value
		Tertile 1 ($<2.0 \text{ }\mu\text{g/dL}$)	Tertile 2 ($2.0\text{--}3.7 \text{ }\mu\text{g/dL}$)	Tertile 3 ($\geq 3.8 \text{ }\mu\text{g/dL}$)	
All deaths	4422	631	1340	2451	..
Cardiovascular disease deaths	1801	218	552	1031	..
Ischaemic heart disease deaths	988	112	284	592	..
Men	47.9%	24.6%	49.2%	68.3%	<0.0001
Ethnic origin					
White	77.1%	78.4%	78.8%	74.2%	0.02
Black	10.2%	9.1%	9.2%	12.2%	0.004
Mexican-American	5.2%	4.8%	5.0%	5.7%	0.15
High-school education	76.2%	84.5%	78.1%	66.6%	<0.0001
Income >US\$20 000	68.1%	72.3%	69.7%	62.6%	<0.0001
Urban residence	47.8%	45.0%	48.2%	50.2%	0.21
Current smoker	34.9%	23.0%	33.0%	47.8%	<0.0001
Former smoker	21.9%	18.3%	22.4%	24.9%	0.0001
Alcohol intake (drinks per month)					
Four or fewer	63.2%	73.3%	62.3%	54.8%	<0.0001
More than four	36.8%	26.7%	37.7%	45.2%	<0.0001
Physical activity (per month)					
None	25.8%	22.8%	24.6%	29.8%	<0.0001
One to 14 times	37.5%	39.5%	37.2%	35.9%	0.07
15 or more times	36.7%	37.7%	38.2%	34.3%	0.06
Hypertension	17.5%	9.6%	18.0%	24.3%	<0.0001
Diabetes	16.5%	12.0%	18.0%	19.2%	<0.0001
Healthy eating index					
First tertile	33.3%	30.4%	31.8%	37.5%	<0.0001
Second tertile	33.3%	35.4%	31.2%	33.5%	0.20
Third tertile	33.4%	34.2%	37.0%	29.0%	<0.0005
Body-mass index					
Normal weight ($<25.0 \text{ kg/m}^2$)	44.6%	49.4%	42.8%	42.0%	<0.0002
Overweight ($25.0\text{--}29.9 \text{ kg/m}^2$)	33.0%	27.0%	24.5%	36.9%	<0.0001
Obese ($\geq 30.0 \text{ kg/m}^2$)	22.4%	23.6%	22.7%	21.1%	0.13
Age (years)*	44.1	37.8	44.8	48.2	<0.0001
Total cholesterol (mg/dL)*	203.8	195.7	204.7	210.6	<0.0001
HbA _{1c} (%)*	5.35	5.21	5.38	5.46	<0.0001
Serum cotinine (ng/mL)†	1.79	0.64	1.69	4.95	<0.0001
Urinary cadmium ($\mu\text{g/g}$)‡	0.33	0.24	0.33	0.47	<0.0001

Data are number, %, or mean. Percentages and means are weighted to match the age, sex, and ethnic origin distribution of the US population. To convert values for lead from $\mu\text{g/dL}$ to $\mu\text{mol/L}$, multiply by 0.0483. p values represent tests for linear trend across lead tertiles. *Age, total cholesterol, and glycated haemoglobin (HbA_{1c}) were treated as continuous variables. †Values represent geometric means. ‡Urinary cadmium is adjusted for urinary creatinine.

Table 1: Baseline characteristics by tertiles of concentrations of lead in blood and deaths in the NHANES-III mortality follow-up study, 1988–94 to 2011 (n=14 289)

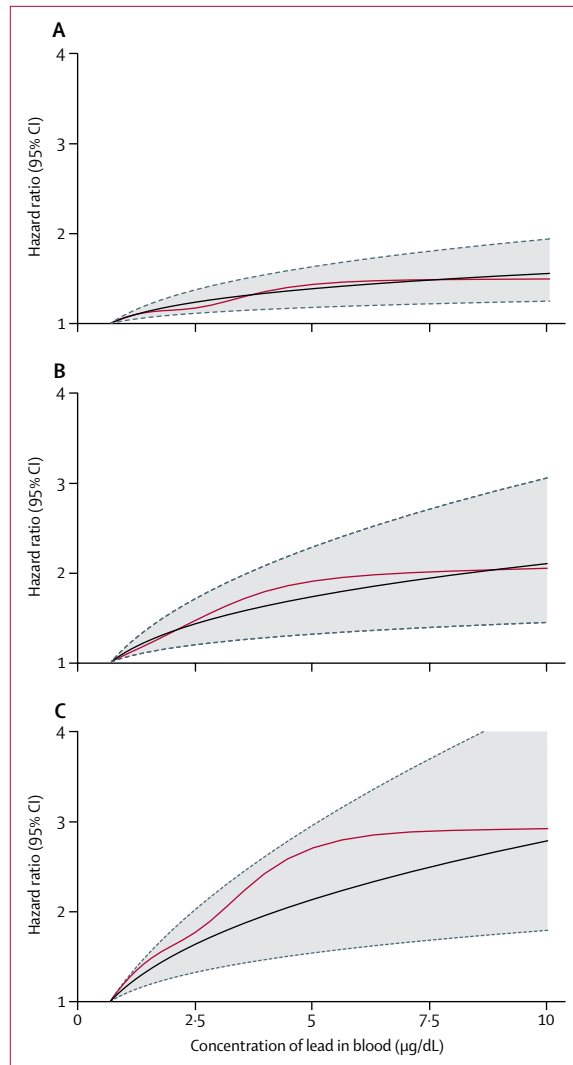


Figure 1: Dose-response curves for concentrations of lead in blood and mortality

Adjusted hazard ratios (black lines) with 95% CIs (hatched lines) and restricted cubic spline (red lines) for (A) all-cause mortality, (B) cardiovascular disease mortality, and (C) ischaemic heart disease mortality.

attributable fractions using a substitution method proposed by Daly.²⁴ We evaluated the proportional hazards assumption using Schoenfeld residuals;²⁵ none of the models violated the assumption. Finally, we accommodated the complex survey design of NHANES-III using SUDAAN (version 10.0.1) to provide weighted national estimates and Taylor linearisation to obtain associated variance estimates.²⁶

We also did several secondary analyses. To assess the effects of low-level exposure to lead, we restricted our analysis to participants who had amounts of lead in blood lower than 5 µg/dL (<0.24 µmol/L). We tested for confounding of concentrations of lead in blood and hypertension for all-cause mortality and cardiovascular disease mortality by examining the change in the

estimates for amounts of lead in blood in models with and without hypertension. We also investigated the change in estimates for hypertension in models with and without concentrations of lead in blood. Next, we assessed whether characterising potential confounders—eg, diabetes, HDL, hypertension, alcohol intake, household income—differently than in our primary analyses would alter our results appreciably. We also investigated the effect of secular trends on HRs for concentrations of lead in blood by examining NHANES-III phase 1 (1988–91) and phase 2 (1991–94) data separately. Finally, we assessed effect modification of the relation between concentration of lead in blood and key characteristics (eg, sex, age, urban residence,²⁷ ethnic origin, smoking status, and diabetes).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The sample population included 18825 adults aged 20 years or older. Of these, 17030 (90%) had a medical examination and home interview. 1419 (6%) participants were missing a result for either concentration of lead in blood or cadmium in urine, 1314 (7%) were missing other covariates, and eight (0.1%) had insufficient identifiers to link with the National Death Index. Thus, 14289 (76%) participants were included in this analysis. 1150 (9%) individuals had concentrations of lead in blood below the level of detection and had an amount of 0.7 µg/dL (0.034 µmol/L) imputed. Characteristics of participants who were included in the analysis differed from those with missing data for some characteristics, such as ethnic origin, alcohol intake, and the prevalence of diabetes (appendix p 2).

During median follow-up of 19.3 years (IQR 17.6–21.0), 4422 participants died; 1801 (38%) were attributable to cardiovascular disease and 988 (22%) to ischaemic heart disease. Concentrations of lead in blood, which ranged from 1.0 µg/dL to 56 µg/dL (0.048 µmol/L to 2.70 µmol/L), were right-skewed with a geometric mean at baseline of 2.71 µg/dL (geometric SE 0.131); 3632 (20%) participants had amounts of lead in blood of 5 µg/dL or higher (≥0.24 µmol/L). Participants who had the highest concentrations of lead in blood were older, less educated, and more likely to be male, to smoke cigarettes, to consume larger amounts of alcohol, and to have less healthy diets (table 1). Participants who had high concentrations of lead in blood were also more likely to have elevated amounts of cholesterol in serum and higher rates of hypertension and diabetes.

Analysis of restricted cubic splines indicated that adjusted HRs were steeper at lower concentrations of lead in blood than at higher concentrations (figure 1).

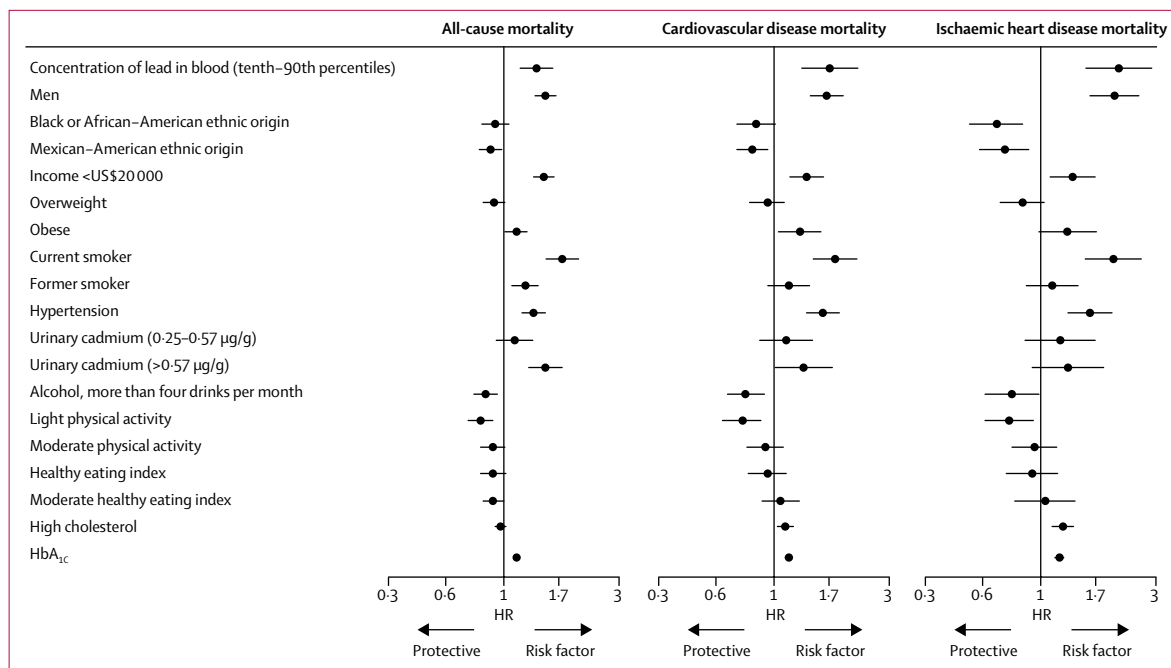


Figure 2: Risk factors for all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality
 Adjusted hazard ratios (HRs) are shown as dots and 95% CIs as horizontal lines. HRs for cholesterol and glycated haemoglobin (HbA_{1c}) refer to an IQR-sized increase (56 mg/dL and 0.7%, respectively). HRs for age represent a 10-year increase.

A model was fitted using the log₁₀ of measurements of lead in blood in the proportional hazards model and adjusted HRs and 95% CIs were calculated for all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality, as well as for other characteristics (figure 2). An increase in the concentration of lead in blood from 1.0 µg/dL to 6.7 µg/dL (0.048 µmol/L to 0.324 µmol/L), which represents the tenth to 90th percentiles, was associated significantly with all-cause mortality (HR 1.37, 95% CI 1.17–1.60), cardiovascular disease mortality (1.70, 1.30–2.22), and ischaemic heart disease mortality (2.08, 1.52–2.85; table 2).

Population attributable fractions were calculated to show the proportional reduction in all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality that would occur if recorded concentrations of lead in blood were reduced to 1.0 µg/dL or lower (≤0.048 µmol/L). The adjusted population attributable fraction for all-cause mortality was 18% (95% CI 10.9–26.1), equivalent to 412 000 (95% CI 250 000–598 000) deaths each year (table 2). Adjusted population attributable fractions were 28.7% (95% CI 15.5–39.5) for cardiovascular disease mortality and 37.4% (23.4–48.6) for ischaemic heart disease mortality, equivalent to 256 000 cardiovascular disease deaths and 185 000 ischaemic heart disease deaths annually (figure 3). In analyses restricted to participants who had concentrations of lead in blood lower than 5 µg/dL (<0.24 µmol/L), an increase in lead in blood from 1.0 µg/dL to 5.0 µg/dL (0.048 µmol/L to 0.242 µmol/L),

	Unadjusted HR (95% CI)	HR (95% CI)	Population attributable fraction (95% CI)	Avoidable deaths (95% CI)
All-cause mortality	3.79 (3.18–4.50)	1.37 (1.17–1.60)	18.0% (10.9–26.1)	412 000 (250 000–598 000)
Cardiovascular disease mortality	4.44 (3.47–5.68)	1.70 (1.30–2.22)	28.7% (15.5–39.5)	256 000 (138 000–352 000)
Ischaemic heart disease mortality	5.31 (4.06–6.93)	2.08 (1.52–2.85)	37.4% (23.4–48.6)	185 000 (116 000–241 000)

All models are adjusted for age (continuous and age-squared), sex, household income (<US\$20 000 or ≥\$20 000 per year), ethnic origin (white, black, or Mexican-American), body-mass index (normal [$<25.0 \text{ kg/m}^2$], overweight [$25.0\text{--}29.9 \text{ kg/m}^2$], or obese [$\geq 30.0 \text{ kg/m}^2$]), smoking status (never, current, or former), hypertension (systolic blood pressure $\geq 140 \text{ mm Hg}$ or diastolic blood pressure $\geq 90 \text{ mm Hg}$), urinary cadmium (tertiles [$\mu\text{g/g}$]), alcohol consumption (four or fewer or more than four drinks per month), physical activity in previous month (none, one to 14 times, 15 or more times), healthy eating index (tertiles), serum cholesterol (continuous), and glycated haemoglobin (continuous). Hazard ratios (HRs) for continuous concentrations of lead in blood represent the risk for an increase in log-transformed concentrations of lead in blood from 1.0 µg/dL to 6.7 µg/dL (0.048 µmol/L to 0.324 µmol/L (tenth to 90th percentiles).

Table 2: Adjusted HRs, population attributable fractions, and avoidable deaths from all causes, cardiovascular disease, and ischaemic heart disease in the NHANES-III mortality follow-up study (n=14 289)

which represents the tenth to 80th percentiles, was associated significantly with all-cause mortality (HR 1.38, 95% CI 1.15–1.66), cardiovascular disease mortality (1.95, 1.46–2.60), and ischaemic heart disease mortality (2.57, 1.56–4.52).

In secondary analyses, no appreciable attenuation or confounding of estimates for concentration of lead in blood or hypertension was noted when these variables were included or excluded consecutively in our primary model. The results of our primary analysis did not change substantially when we made several adjustments:

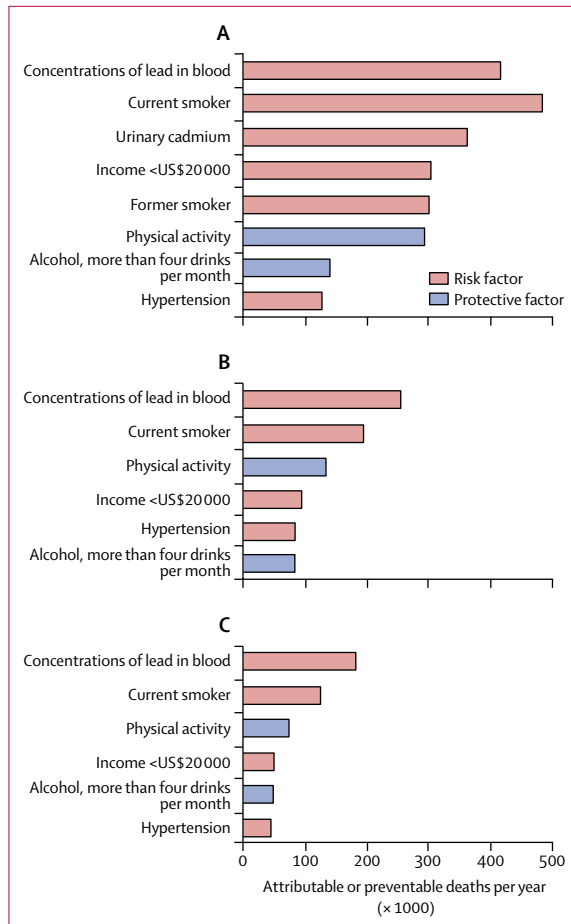


Figure 3: Attributable deaths associated with selected modifiable risk factors in the US population

Panels show deaths from (A) all causes, (B) cardiovascular disease, and (C) ischaemic heart disease. Modifiable risk factors are presented in red and protective factors in blue. Deaths were calculated from population attributable fractions and average mortality in the USA from 1988 to 2011. Only significant risk factors are represented.

characterised diabetes as a categorical instead of a continuous measure; adjusted for both HDL and cholesterol; adjusted for hypertension status (ie, systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg and use of anti-hypertension drugs); adjusted for household income using the poverty index ratio (instead of $< \$20\,000$ or $\geq \$20\,000$ per year); characterised hypertension as a continuous measure of both systolic blood pressure and diastolic blood pressure instead of a categorical measure; characterised alcohol intake as one or no drink per day versus more than one drink per day (instead of four or fewer drinks versus more than four drinks per month); or excluded participants who had a concentration of lead in blood lower than $1.0\ \mu\text{g/dL}$ ($0.048\ \mu\text{mol/L}$; appendix pp 3, 4). Median concentrations of lead in blood decreased by 22% from NHANES-III phase 1 (1988–91) to phase 2 (1991–94). Consistent with the steeper increase in relative risk, at lower concentrations

of lead in blood, the rate of increase in relative risk was steeper for participants who were studied during NHANES-III phase 2 (1991–94) than phase 1 (1988–91; appendix p 4).

Examination of effect modification of the relation between concentration of lead in blood and key characteristics showed that HRs for participants younger than 50 years were significantly larger than were those for participants aged 50 years or older, for all-cause mortality (HR 2.24, 95% CI 1.50–3.34 vs 1.53, 1.18–1.98; $p=0.003$ for interaction), cardiovascular disease mortality (2.93, 1.60–5.36 vs 2.08, 1.35–3.19; $p=0.01$), and ischaemic heart disease mortality (4.68, 2.42–9.05 vs 2.46, 1.51–4.01; $p=0.02$). The HR for cardiovascular disease mortality was significantly larger for non-smokers than smokers (HR 2.19, 95% CI 1.47–3.26 vs 1.32, 0.86–2.05; $p=0.03$ for interaction).

Discussion

Our findings suggest that, of 2.3 million deaths every year in the USA, about 400 000 are attributable to lead exposure, an estimate that is about ten times larger than the current one.²⁸ The key reason for this difference is because the previous estimate assumed cardiovascular disease was only evident at concentrations of lead in blood as low as $5\ \mu\text{g/dL}$.²⁸ Our findings show that concentrations of lead in blood lower than $5\ \mu\text{g/dL}$ ($< 0.24\ \mu\text{mol/L}$) are associated with all-cause mortality, cardiovascular disease mortality, and ischaemic heart disease mortality. In other studies, amounts of lead in blood lower than $10\ \mu\text{g/dL}$ ($< 0.483\ \mu\text{mol/L}$) were associated with cardiovascular disease mortality,^{7,9,10} but our study is the first to test whether the relation with cardiovascular disease mortality was evident in a population with concentrations of lead in blood below $5\ \mu\text{g/dL}$ ($< 0.24\ \mu\text{mol/L}$). These results suggest that low-level lead exposure is an important, largely overlooked, risk factor for death in the USA, particularly for cardiovascular disease deaths.

Our results accord with those of other population-based studies showing that concentrations of lead in either blood or bone are risk factors for all-cause mortality and cardiovascular disease mortality.^{5–13} A significant association was noted between increased lead exposure and all-cause mortality in six prospective studies,^{6,7,9,11–13,29} and a significant association was reported between increased lead exposure and cardiovascular mortality in five of six prospective studies.^{6,7,9,11–13} No association between concentration of lead in blood and cardiovascular disease mortality was noted after adjustment for other risk factors in a study²⁹ that only included 19 deaths from cardiovascular disease.

In our study, the estimated number of deaths from all causes and cardiovascular disease that were attributable to concentrations of lead in blood were surprisingly large; indeed, they were comparable with the number of deaths from current tobacco smoke exposure. The HR

for all-cause mortality from tobacco exposure was larger than that for concentration of lead in blood, but only 20% of the US population smoked tobacco. By contrast, 90% of participants were exposed to lead; a smaller relative risk for a prevalent exposure can result in a larger population attributable fraction.

Concentrations of lead in blood lower than 5 µg/dL (<0.24 µmol/L) were associated with an increased risk of cardiovascular disease mortality. This result contrasts with conclusions of the National Toxicology Report,⁵ which noted that evidence was limited for an association between amounts of lead in blood less than 10 µg/dL and increased cardiovascular-related mortality. We also reported that risk coefficients for cardiovascular disease in the subset of participants with concentrations of lead in blood lower than 5 µg/dL (<0.24 µmol/L) were generally larger than coefficients in the total sample. Although the rate of increase in mortality was greatest with low amounts of lead in blood, HRs indicate that the risk of cardiovascular disease mortality is rising with higher amounts of lead in blood, but at a diminished rate. These results, which accord with those of an earlier study in this same cohort but of shorter duration,⁷ should not be surprising; despite the striking reductions in concentrations of lead in blood over the past 50 years, amounts found nowadays in adults are still ten times to 100 times higher than people living in the preindustrial era (ie, 700–1000 years ago).³⁰ Moreover, the assumption that there are thresholds for specific toxicants—eg, lead, tobacco, and airborne particles—is slowly eroding.³¹

The cardiovascular toxicity of lead stems from various mechanisms. In experimental studies, lead causes hypertension, results in oxidative stress and inflammation, diminishes endothelium relaxation, and promotes development of atherosclerosis and thrombosis.³⁴ In human beings, lead is a recognised risk factor for hypertension and has been associated with peripheral arterial disease, electrocardiographic abnormalities, and left-ventricular hypertrophy.^{4,10} In a randomised controlled trial of patients who had had a myocardial infarction, chelation with EDTA and multivitamin therapy led to an 18% reduction in cardiovascular events; patients with diabetes in the trial had a 34% reduction in cardiovascular events.³² Collectively, these findings suggest, but do not prove, that atherosclerosis and hypertension both could serve as underlying mechanisms for the cardiovascular toxicity of lead.

Our study has limitations. The key limitation is that we relied on baseline measures of exposure to predict death over the subsequent two decades. Some measures (eg, concentration of lead in blood) might be more stable than other risk factors (eg, diet). Lead that is circulating in whole blood of adults is an indicator of both past and ongoing exposures. Serial measures of concentrations of lead in blood or bone, which are better indicators of cumulative exposure than one concentration of lead in

blood,⁹ would have strengthened this study; indeed, our reliance on one measurement for concentration of lead in blood might underestimate the contribution of lead exposure to mortality. Moreover, we relied on death certificates for the underlying cause of death, but they are imperfect. We adjusted for co-exposure to cadmium, but we were not able to adjust for air pollutants or arsenic, both of which are risk factors for cardiovascular disease mortality.³³ Finally, and perhaps most importantly, although we adjusted for an extensive array of potential confounders, we cannot exclude residual confounding that might result in an overestimation of the effect of concentrations of lead in blood, particularly from socioeconomic and occupational factors that were either not measured or measured inadequately. Yet, the shape of the dose-response argues against confounding to account for our results because the confounders, which are correlated positively with amounts of lead in blood, are found primarily in the highest risk groups (table 1); the steepest increase in risk occurs at the lower concentrations of lead in blood.

In conclusion, our study findings suggest that low-level environmental lead exposure is an important risk factor for death in the USA, particularly from cardiovascular disease. It is not surprising that lead exposure is overlooked; it is ubiquitous, but insidious and largely beyond the control of patients and clinicians. Although reducing the amount of lead in blood might cut a patient's risk of cardiovascular disease mortality,³² it is more accurate to view this study as estimating how many deaths might have been prevented if historical exposures to lead had not occurred. Indeed, this study suggests that estimating the contribution of environmental lead exposure is essential to understand trends in cardiovascular disease mortality and develop comprehensive strategies to prevent cardiovascular disease.^{34,35}

Contributors

All authors designed the study, contributed to data interpretation, and wrote the report. PA had access to raw data. SR, PA, and RWH analysed data.

Declaration of interests

We declare no competing interests. BPL serves as an expert witness in plaintiff cases of childhood lead poisoning in Milwaukee and Flint, MI, USA, but he receives no personal compensation.

References

- 1 Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics: 2016 update—a report from the American Heart Association. *Circulation* 2016; **133**: e38–360.
- 2 Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in US deaths from coronary disease, 1980–2000. *N Engl J Med* 2007; **356**: 2388–98.
- 3 Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. *Am J Physiol Heart Circ Physiol* 2008; **295**: H5454–65.
- 4 US Environmental Protection Agency. Air quality criteria for lead (final report, 2006). October, 2006. <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=158823> (accessed Feb 12, 2018).
- 5 National Toxicology Program (NTP). NTP monograph: health effects of low-level lead. June, 2012. https://ntp.niehs.nih.gov/ntp/ohat/lead/final/monographhealtheffectslowlevellead_newissn_508.pdf (accessed Feb 12, 2018).

- 6 Lustberg M, Silbergeld E. Blood lead levels and mortality. *Arch Intern Med* 2002; **162**: 2443–49.
- 7 Menke A, Muntner P, Batuman V, Silbergeld EK, Guallar E. Blood lead below 0–48 µmol/L (10 µg/dL) and mortality among US adults. *Circulation* 2006; **114**: 1388–94.
- 8 Pirkle JL, Schwartz J, Landis R, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *Am J Epidemiol* 1985; **121**: 246–58.
- 9 Schober SE, Mirel LB, Graubard BI, Brody DJ, Flegal KM. Blood lead levels and death from all causes, cardiovascular disease, and cancer: results from the NHANES III Mortality Study. *Environ Health Perspect* 2006; **114**: 1538–41.
- 10 Navas-Acien A, Guallar E, Silbergeld, Rothenberg SJ. Lead exposure and cardiovascular disease: a systematic review. *Environ Health Perspect* 2006; **115**: 472–82.
- 11 Weisskopf MG, Jain N, Nie H, 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. *Circulation* 2009; **120**: 1056–64.
- 12 Khalil N, Wilson JW, Talbot EO, et al. Association of blood lead concentrations with mortality in older women: a prospective cohort study. *Environ Health* 2009; **8**: 15.
- 13 Aoki Y, Brody DJ, Flegal KM, Fakhouri TH, Parker JD, Axelrad DA. Blood lead and other metal biomarkers as risk factors for cardiovascular disease mortality. *Medicine* 2016; **95**: e2223.
- 14 Menke A, Muntner P, Silbergeld EK, Platz EA, Guallar E. Cadmium levels in urine and mortality among US adults. *Environ Health Perspect* 2009; **117**: 190–96.
- 15 Gunter EW, Lewis BG, Koncikowski SM. Laboratory procedures used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. 1996. <https://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/labman.pdf> (accessed Feb 12, 2018).
- 16 Pirkle JL, Brody DJ, Gunter EW, et al. The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys. *JAMA* 1994; **272**: 284–91.
- 17 Hornung RW, Reed LD. Estimates of average concentration in the presence of non-detectable values. *Appl Occup Environ Hyg* 1990; **5**: 46–51.
- 18 Ingram DD, Lochner KA, Cox CS. Mortality experience of the 1986–2000 National Health Interview Survey linked mortality files participants. *Vital Health Stat 2* 2008; **147**: 1–37.
- 19 US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. NHANES I Epidemiologic Follow-up Survey (NHEFS): calibration sample for NDI matching methodology. Sept 17, 2009. https://www.cdc.gov/nchs/data/datalinkage/mort_calibration_study.pdf (accessed Feb 1, 2013).
- 20 Kennedy ET, Ohls J, Carlson S, Fleming K. The healthy eating index; design and applications. *J Am Diet Assoc* 1995; **95**: 1103–08.
- 21 Vander Hoorn S, Ezzati M, Rodgers A, Lopez AD, Murray CJL. Estimating attributable burden of disease from exposure and hazard data. In: Ezzati M, Lopez AD, Rodgers, Murray CJL, eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization, 2004: 2129–40.
- 22 National Center for Health Statistics, Centers for Disease Control and Prevention. National Vital Statistics System: historical data, 1900–1998. Nov 6, 2015. https://www.cdc.gov/nchs/nvss/mortality_historical_data.htm (accessed Feb 12, 2018).
- 23 National Center for Health Statistics, Centers for Disease Control and Prevention. Multiple cause of death data. Dec 20, 2017. <https://wonder.cdc.gov/mcd.html> (accessed Feb 12, 2018).
- 24 Daly L. Confidence limits made easy: interval estimation using a substitution method. *Am J Epidemiol* 1998; **147**: 83–90.
- 25 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; **69**: 239–41.
- 26 Shah VBBB, Bieler GS. SUDAAN user's manual, release 10.01. Research Triangle Park: Research Triangle Institute, 2005.
- 27 Ingram DD, Franco SJ. NCHS urban-rural classification scheme for counties. *Vital Health Stat 2* 2012; **154**: 1–65.
- 28 Institute for Health Metrics and Evaluation (IHME). GBD database, 2016. <http://vizhub.healthdata.org/gbd-compare/#> (accessed Aug 12, 2016).
- 29 Moller L, Kristensen TS. Blood lead as a cardiovascular risk factor. *Am J Epidemiol* 1992; **136**: 1091–100.
- 30 Flegal AR, Smith DR. Lead levels in preindustrial humans. *N Engl J Med* 1992; **326**: 1293–94.
- 31 Lanphear BP. Low-level toxicity of chemicals: no acceptable levels? *PLoS Biol* 2017; **15**: e2003066.
- 32 Lamas GA, Boineau R, Goertz C, et al. EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: the factorial groups results of the Trial to Assess Chelation Therapy. *Am Heart J* 2014; **168**: 37–44.
- 33 Cossleman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015; **12**: 627–42.
- 34 Rosenthal FS, Lanphear BP, Gottesfeld P, et al. Commentary: ISEE call for action for global control of lead exposure to eliminate lead poisoning. *Epidemiology* 2015; **26**: 774–77.
- 35 Ruiz-Hernandez A, Navas-Acien A, Pastor-Barriuso R, et al. Declining exposures to lead and cadmium contribute to explaining the reduction of cardiovascular mortality in the US population, 1988–2004. *Int J Epidemiol* 2017; **46**: 1903–12.