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Lead-associated mortality in the US 1999–2020: a time-stratified analysis of a national cohort

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Objectives: We undertook time-stratified analyses of the National Health and Nutrition Examination Survey in the US to assess time trends (1999–2020) in the associations of blood lead (BL) with blood pressure, mortality, the BL-associated population attributable fraction (PAF).

Methods: Vital status of participants, 20–79 years old at enrolment, was ascertained via the National Death Index. Regressions, mediation analyses and PAF were multivariable adjusted and standardized to 2020 US Census data.

Results: In time-stratified analyses, BL decreased from 1.76 μg/dl in 1999–2004 to 0.93 μg/dl in 2017–2020, while the proportion of individuals with BL < 1 μg/dl increased from 19.2% to 63.0%. Total mortality was unrelated to BL (hazard ratio (HR) for a fourfold BL increment: 1.05 [95% confidence interval, CI: 0.93–1.17]). The HR for cardiovascular death was 1.44 (1.01–2.07) in the 1999–2000 cycle, but lost significance thereafter. BL was directly related to cardiovascular mortality, whereas the indirect BL pathway via BP was not significant. Low socioeconomic status (SES) was directly related to BL and cardiovascular mortality, but the indirect SES pathway via BL lost significance in 2007–2010. From 1999–2004 to 2017–2020, cardiovascular PAF decreased ($P < 0.001$) from 7.80% (0.17–14.4%) to 2.50% (0.05–4.68%) and number of lead-attributable cardiovascular deaths from 53 878 (1167–99 253) to 7539 (160–14 108).

Conclusion: Due to implementation of strict environmental policies, lead exposure is no longer associated with total mortality, and the mildly increased cardiovascular mortality is not associated with blood lead via blood pressure in the United States.

Keywords: blood pressure, cardiovascular mortality, environmental medicine, lead exposure, population science, public health

Abbreviations: γGT, γ-glutamyltransferase; 95% CI, 95% confidence interval; BCd, cadmium concentration in whole blood; BL, lead concentration in whole blood; BMI, body-mass index; BP, blood pressure; eGFR, glomerular filtration rate estimated from serum creatinine, using the race-free Chronic Kidney Disease-Epidemiology Collaboration equation; GBD, global burden of disease; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey; PAF, population attributable fraction; $PM_{2.5}$, fine particulate matter with diameter ≤2.5 μm; SES, socio-economic status; US, United States of America

INTRODUCTION

Lead is a ubiquitous environmental pollutant, which causes hypertension [1,2] and renal dysfunction [3,4], thereby increasing mortality [5–8]. These adverse health effects are thought to be mediated through mechanisms such as oxidative stress and the promotion of atherosclerosis. The 2-year cycles of the US National Health and Nutrition Examination Survey (NHANES) include a nationally representative sample of US population. As a result of environmental policies in the United States [9], blood lead (BL) fell from 13.1 μg/dl in NHANES II (1976–1980) [10] to 2.76 μg/dl in NHANES III (1988–1994) [10] and further to 1.64 μg/dl in NHANES IV (1999–2002) [11,12]. Studies from birth cohorts showed confirmatory decline in the NHANES and outside the United States [13,14]. Currently, the primary exposure route of the general population runs via respirable lead-contaminated particulate,

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containing lead deposited in the 20th century [15,16]. Particles with an aerodynamic diameter of <100 nm, part of the ≤2.5 μm ($PM_{2.5}$) fraction, pass the air–blood barrier in lung alveoli and are bodywide distributed via the blood stream [15]. Over 90% of lead entering the body accumulates in bone, from where it is recirculated with a half-life of 20–25 years [17]. BL therefore reflects exposure over the past 1–2 months and lead recirculated from bone stores [17].

Most NHANES reports showed association of total or cardiovascular mortality with BL [5–8], but to our knowledge none did account for the fall in BL over time. To address this knowledge gap, we analyzed time trends (1999–2020) in successive NHANES cycles in the associations of BL with blood pressure (BP) – the presumed causal mediator [1,18] – with mortality, Furthermore we assessed time trends in the BL-related population attributable fraction (PAF) and number of attributable deaths (NAD).

METHODS

Study design and participants

NHANES is a multistage stratified survey designed to provide detailed information on the health and nutritional status of a nationally representative sample of noninstitutionalized individuals in the United States. Protocols were approved by the Institutional Review Board of the Centers for Disease Control and Prevention. At all waves participants provided informed written consent. Data from ten 2-year study cycles (1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, 2017–2018) were analyzed. NHANES 2019–2020 was postponed due to the COVID-19 pandemic, but a nationally representative cohort was constructed including participants from the 2017 to March 2020 cycle. NHANES provides statistical weights that account for survey design (including oversampling), survey nonresponse, and poststratification adjustment to ensure that estimates are representative of the noninstitutionalized civilian US population. The main database (Fig. 1) included 33 286 individuals, aged 20–79 years at enrollment, who had been examined during survey cycles 1999–2018 and who had a valid baseline BL measurement and known vital status on 31 December 2019. To refine the time trends in BL and the BL-associated PAF and NAD, 1520 individuals included in the 2019–2020 cycle were analyzed as well (Figure 1).

Measurements

BL was measured by inductively coupled plasma mass spectrometry. The lower detection limits were 0.30 μg/dl (1999–2004), 0.25 μg/dl (2005–2012) and 0.07 μg/dl (2013–2020). A scaling factor of $1/\sqrt{2}$ was applied for BL levels below the detection limit. The BL threshold assumed

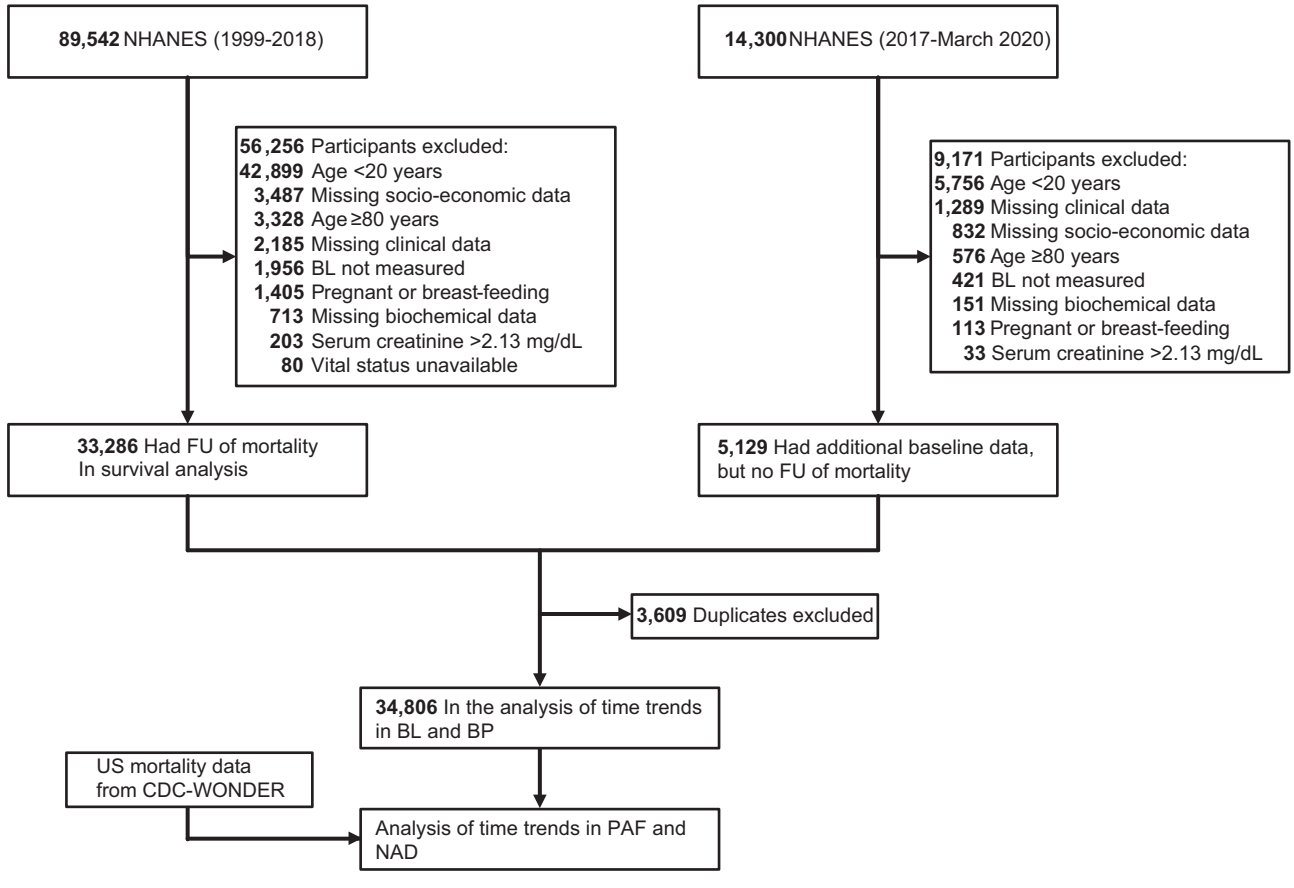

FIGURE 1 Flow chart. The flow chart showing the selection of NHANES participants. NHANES 2019–2020 was postponed due to COVID-19 pandemic and a nationally representative cohort was constructed with participants from 2017 to March 2020 cycle. Mortality for NHANES through record linkage was available until 2019. To estimate the population attributable fraction (PAF) and the number of attributable deaths for the 2017–2020 interval, the hazard ratios derived from NHANES data were applied to the National Vital Statistics System, Mortality 1999–2020 on CDC WONDER Online Database (accessed 13 July 2023).

to confer risk in the categorical analysis was 1 μg/dl, which according to the Global Burden of Disease Investigators is lower than the preindustrial BL level (2 μg/dl) [18]. eGFR was calculated for serum creatinine by the 2021 race-free Chronic Kidney Disease-Epidemiology Collaboration equation [19].

Outcomes

Staff members of the National Center for Health Statistics linked NHANES participants to the underlying cause of death in the National Death Index by means of a series of identifiers, such as social security number and date of birth, using probabilistic matching criteria. The underlying cause of death was obtained using codes from the International Classification of Diseases, version 10. The endpoints of interest in the current study were total, cardiovascular (I00–I09, I11, I13, I20–I51; I60–I69) and cardiac mortality (I00–I09, I11, I13, I20–I51). Deaths contributing to total mortality, but not classified as cardiovascular, were aggregated as noncardiovascular deaths, including cancer mortality (C00–C97), and analyzed as control.

Statistical analysis

Statistical analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC). In compliance with the statistical guidelines for NHANES data, all observations with positive sampling weights were included in the main dataset, and domain (subset) analyses were conducted with consideration of sampling design and weight. Categorical variables were described as number or weighted percentage and continuous variables as weighted arithmetic or geometric mean. Between group comparison of continuously distributed and categorical variables were done by the large sample Z test and Rao–Scott χ^2 test, respectively.

The distributions of BL, blood cadmium (BCd), serum cotinine and γ-glutamyltransferase were logarithmically transformed (base 4.0) to approximate normality and to increase the interpretability as every one-unit increment in the transformed variable indicates a fourfold increase. The associations of BP or hypertension with BL were evaluated by multivariable-adjusted linear or logistic regression, including the 2017–2020 data. The secular trends in mortality were modelled by multivariable linear regression analysis.

Associations between mortality and BL, analyzed as continuously distributed variable or categorized per the 1 μg/dl BL threshold, were modelled using weighted multivariable Cox regression, excluding the 2017–2020 data, for which mortality was incompletely recorded. To check the proportional hazard assumption, time-by-covariable interaction terms were tested. To assess the time-dependence of the association of mortality with BL, HRs and their 95% confidence intervals (95% CI) were generated for each survey cycle separately and combined using a fixed-effect meta-analysis weighted by the inverse variance. Other sensitivity analyses addressed the associations with BL in subgroups. To estimate the disease burden conferred by lead exposure, the multivariable-adjusted weighted PAF was computed from HRs expressing the risk per the 1 μg/dl BL threshold, using published formula [20]. PAF and NAD were calculated from the annualized cardiovascular and cardiac mortality and the number of deaths in participants with BL >1.00 μg/dl as proportion of all deaths [21]. The 95% CI of PAF and NAD was generated by a bootstrap procedure with 1000 repetitions and 1 : 1 resampling with replacement. Finally, BP, hypertension, and low socio-economic status (SES) defined as poverty index of ≤1.3 and less than high school education were evaluated as potential mediators linking BL to cardiovascular and cardiac mortality, using the SAS CAUSALMED procedure.

RESULTS

Baseline characteristics of participants

Table 1 lists the baseline characteristics of the study participants. The 34 806 individuals included 50.1% women. Mean age was 45.7 years and the geometric mean BL 1.19 μg/dl (interquartile range: 0.74–1.88 μg/dl). Analyzed compared with nonanalyzed NHANES participants included fewer women, more whites, better educated and more affluent people, and less patients with a history of cardiovascular disease (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C437), but geometric mean BL weighted for the sampling strategy was similar in both groups (1.19 vs. 1.18 μg/dl; $P = 0.47$).

Analysis of NHANES participants with linked death record

Median follow-up of 33 286 participants, for whom mortality data were collected from enrollment until 31 December 2019, was 10.3 years (10th–90th percentile interval: 2.6–18.2 years). Among these 33 286 participants, 4010 (12.0%) deaths occurred: 1159 (3.48%), 964 (2.90%), 2851 (8.57%), and 1047 (3.15%) due to cardiovascular, cardiac and noncardiovascular diseases and cancer, respectively. The multivariable-adjusted HRs expressing the risk of death for a fourfold BL increment were 1.04 (95% CI: 0.92–1.17; $P = 0.52$) for total mortality, 1.44 (95% CI: 1.20–1.72; $P = 0.001$) and 1.52 (95% CI: 1.25–1.84; $P < 0.001$) for cardiovascular and cardiac mortality, and 1.06 (95% CI: 0.83–1.36; $P = 0.27$) and 0.92 (95% CI: 0.78–1.07; $P = 0.65$) for noncardiovascular and fatal cancer. While accounting for the competing risk of noncardiovascular or cancer mortality, the adjusted HRs expressing the cardiovascular mortality risk for a 4–fold BL increment were 1.38 (95% CI: 1.20–1.59) and 1.36 (95% CI: 1.18–1.57), respectively. The associations between cardiovascular mortality and BL in various subgroups are listed in Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C437. Significant stratum-by-BL interactions were noted for sex (women vs. men: 1.31 vs. 1.50; $P < 0.001$), Hispanics vs. Whites (1.53 vs. 1.37; $P = 0.01$), old (≥60 years) vs. young (20–39 years) participants (1.27 vs. 2.88; $P = 0.004$), poverty index >3.5 vs. ≤1.3 (1.35 vs. 1.55; $P < 0.001$), and eGFR ≥60 vs. < 60 ml/min/1.73 m^2 (1.50 vs. 1.20; $P = 0.04$). Findings were generally consistent when the HRs were generated by the 1 μg/dl threshold (Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C437).

In a time-stratified approach, Fig. 2 shows the distribution of BL and absolute mortality rates by BL tertiles, and the weighted and multivariable-adjusted HRs for total, cardiovascular and cardiac mortality in relation to BL. The examination cycles ranged from 1999–2000 to 2013–2014 for total

TABLE 1. Baseline characteristics (1999–2020) of 34 806 participants

Characteristic	Estimate[a]	Characteristic	Estimate[a]
Sex, %[b]		Comorbidities, %	
Women	50.1	Hypertension[d]	31.4
Men	49.9	Diabetes[d]	11.3
Ethnicity, %[b]		Ischemic heart disease[d]	5.0
White	69.7	Stroke[d]	2.2
Black	10.4	Chronic heart failure[d]	1.9
Hispanic	13.4	On drug treatment, %	
Asian	6.6	Blood-pressure lowering[d]	22.5
Educational attainment, %[b]		Lipid lowering[d]	14.8
Less than high school	39.5	Antidiabetic agents[d]	7.2
High school	31.4	Clinical measurements	
College or equivalent	29.1	Age, years[b,e]	45.7
Poverty index, %[b,c]		Body-mass index, kg/m^2[d,e]	28.8
≤1.3	20.0	Waist circumference, cm[d,e]	98.4
1.3–3.5	35.4	Systolic blood pressure, mmHg[d,e,f]	121.6
>3.5	44.6	Diastolic blood pressure, mmHg[d,e,f]	71.9
Smoking status, %[b]		Heart rate, bpm[d,e]	72.2
Never	50.8	Biochemical measurements	
Past	21.2	Glycated hemoglobin, %[e,f,h]	5.6
Current	28.0	Total serum cholesterol, mg/dl[e,f,h]	196.5
Alcoholic drinks per week, %[d]		HDL serum cholesterol, mg/dl[e,f,h]	52.9
<1	26.8	Total-to-HDL cholesterol ratio	4.02
1–6	16.2	Serum creatinine, mg/dl[e,f,h]	0.86
≥7	57.0	eGFR, ml/min/1.73 m^2	98.1
Categorized body-mass index, %[d]		Serum cotinine, μg/l[g,h]	0.38
<25 kg/m^2	30.5	Serum γ-glutamyltransferase, U/l[g,h]	21.7
25–30 kg/m^2	33.6	Cadmium in blood, μg/l[g,h]	0.35
>30 kg/m^2	35.9	Lead in blood, μg/dl[g,h]	1.19

[a]All estimates, percentages and arithmetic and geometric means, are weighted to match 2020 US Census by ethnicity, sex, and five-year age categories. The analysis includes 34 806 individuals, combining 11 NHANES cycles from 1999–2000 until 2017–March 2020 (Fig. 1).
[b]At the baseline home visit baseline demographic information was collected, including self-reported ethnicity, sex, age, household income, educational attainment, and smoking status.
[c]The poverty index is the ratio of family income to poverty as defined in each survey year by the Department of Health and Human Services, higher values indicating greater affluence.
[d]Information on body-mass index (body weight in kilogram divided by height square in meters), waist circumference, blood pressure, heart rate, alcohol consumption, medical history, and prescription drug use was obtained during the medical examination.
[e]Values are weighted arithmetic means.
[f]Blood pressure was measured by the auscultatory method after participants had rested quietly in a seated position for five minutes. Three consecutive blood pressure readings were obtained. If a blood pressure measurement was interrupted or incomplete, a fourth attempt was made. The average of all available readings was used for analysis. The glomerular filtration rate was calculated from serum creatinine by the 2021 race-free Chronic Kidney Disease-Epidemiology Collaboration equation.
[g]The distributions of γ-glutamyltransferase (index of alcohol intake), serum cotinine (index of first- and second-hand inhalation of tobacco smoke), blood lead and blood cadmium were logarithmically transformed (base 4.0) to approximate normality and to increase the interpretability as every one-unit increment in the transformed variable indicates a fourfold increase. Values are weighted geometric means.
[h]To convert standard into SI units, multiply by 5.05 for glycated hemoglobin (% to mmol/mol), by 0.0259 for cholesterol (mg/dl to mmol/l), by 88.4 for creatinine (mg/dl to μmol/l), by 0.0167 for γ-glutamyltransferase (from U/l to μkat/l), by 8.90 for cadmium (from μg/l to nmol/l), and by 0.0483 for lead (from μg/dl to μmol/l).

mortality and from 1999–2000 to 2007–2008 for cardiovascular and cardiac mortality. Later cycles were not analyzed, because death rates were less than 2.5%. The pooled HRs were 1.05 (95% CI: 0.93–1.17; $P = 0.43$) for total mortality and 1.23 (95% CI: 1.00–1.51; $P = 0.05$) and 1.30 (95% CI: 1.05–1.62; $P = 0.02$) for cardiovascular and cardiac mortality, respectively. The *P*-values for the decreasing time trends in the HRs were 0.77, 0.12 and 0.20 for total, cardiovascular and cardiac mortality, respectively (Fig. 2).

The natural direct and indirect contribution of BL to cardiovascular and cardiac mortality were explored with time-stratification (1999–2002, 2003–2006, and 2007–2010). Figure 3a–d shows that the HRs signifying the direct contribution of BL to cardiovascular and cardiac mortality were significant ($P \leq 0.03$) in the 1999–2002 and 2003–2006 cycles, but no longer in the 2007–2010 cycle ($P \geq 0.90$), while the indirect contributions mediated via systolic BP ($P \geq 0.07$) or hypertension ($P \geq 0.53$) were not significant in any cycle. Low SES was associated with higher BLs compared with the remainder of the study population (1999–2002: 1.97 vs. 1.65 μg/dl; 2003–2006: 1.83 vs. 1.48 μg/dl; 2007–2010: 1.51 vs. 1.29 μg/dl; $P < 0.001$ for all). Low SES was associated with an increased risk of cardiovascular and cardiac mortality (Figure 3, Panels E-F), while the indirect associations running via BL were significant for the 1999–2002 and 2003–2006 cycles ($P \leq 0.04$), but not for the 2007–2010 cycle ($P \geq 0.74$).

Analysis of NHANES participants with extended baseline data

BL decreased from 1.76 μg/dl in 1999–2004 to 0.93 μg/dl in 2017–2020, while the percentage of individuals with BL <1 μg/dl increased from 19.2% to 63.0% (Fig. 4a). Trends were similar for BCd and serum cotinine (Figure 4b). The BL decline in BL over time was consistent, considering ethnicity, sex, age groups, educational attainment, poverty index and smoking status (Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C437). Trends were similar for BCd and serum cotinine (Figure 4b, http://links.lww.com/HJH/C437).

In multivariable-adjusted analyses spanning the 1999–2020 period, lead exposure was associated with higher BP; the association sizes for a fourfold BL increment amounted to 1.14 (95% CI: 0.56–1.11; $P < 0.001$) systolic and 0.68 mmHg

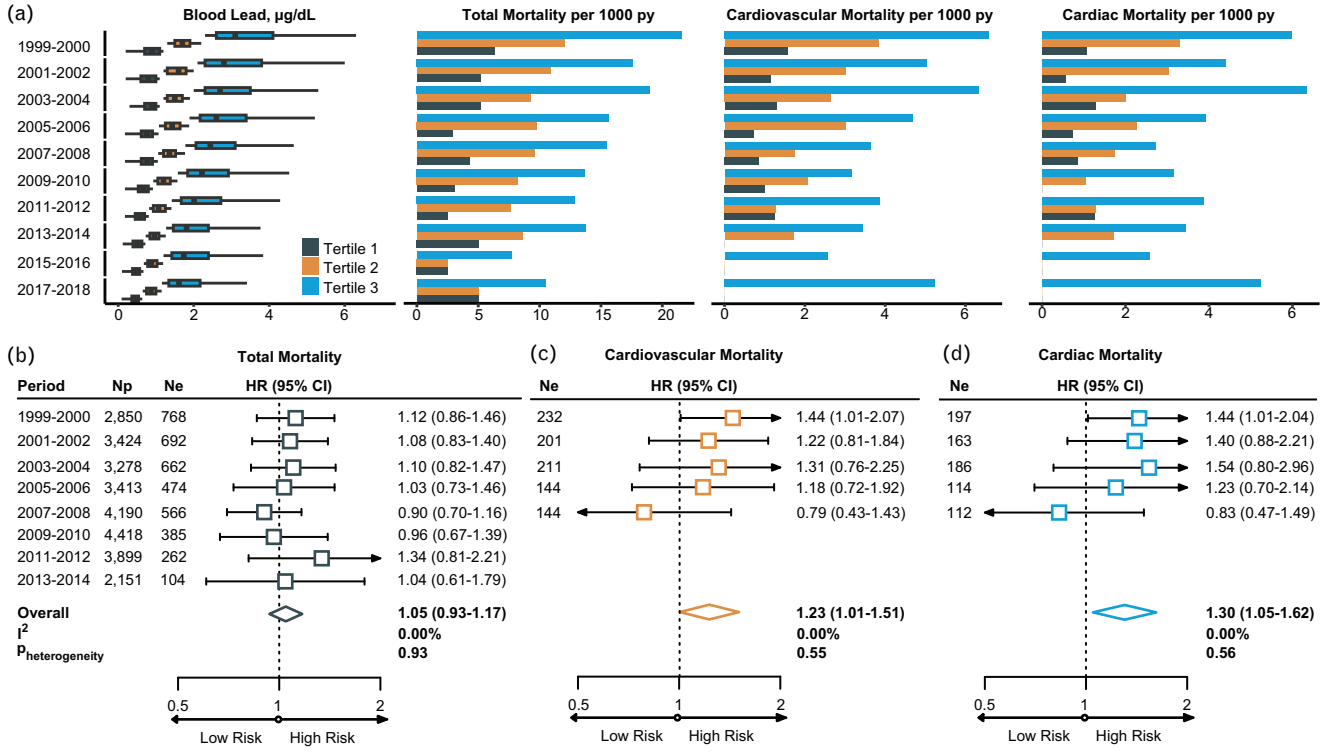

FIGURE 2 Distribution of blood lead and mortality rates by thirds of blood lead and hazard ratios by survey cycle. Distribution of blood lead and mortality rates by thirds of blood lead (a), and hazard ratios (HRs) for total (b), cardiovascular (c) and cardiac (d) mortality express the risk associated with a fourfold blood lead increment. Hazard ratios are adjusted for ethnicity, sex, systolic and diastolic blood pressure, body-mass index, serum cotinine and γ glutamyltransferase, total and high-density lipoprotein serum cholesterol, glycated hemoglobin, cadmium in blood, diabetes, treatment with blood pressure and lipid-lowering drugs, educational attainment, and the poverty index. The examination cycles analyzed range from 1999–2000 to 2013–2014 for total mortality and from 1999–2000 to 2007–2008 for cardiovascular and cardiac mortality, each standardized to 2020 US Census data by ethnicity, sex, and 5-year age category. Later cycles are not analyzed, because the total, cardiovascular and cardiac death rates are less than 48/2024 (2.37%), 101/4418 (2.29%) and 82/4418 (1.86%), respectively. Squares and horizontal lines represent the hazard ratio and 95% confidence interval for each survey cycle. Diamonds represent the pooled estimates with 95% confidence interval weighted for the inverse of the variance in a fixed-effect meta-analysis. The *P* values for time trends in the hazard ratios over the examination cycles are 0.77, 0.12, and 0.20 for total, cardiovascular, and cardiac mortality, respectively. Py denotes person-year, Np number of participants at risk, and Ne the number of deaths.

(95% CI: 0.26–1.11; $P < 0.01$) diastolic (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C437). The associations between systolic BP and BL with effect sizes expressed for a fourfold BL increment were stronger in Blacks than Whites (+2.20 vs. +1.24 mmHg; $P = 0.001$), in old (≥60 years) vs. young (20–39 years) participants (+3.22 vs. +0.27 mmHg; $P = 0.001$), in diabetic vs. nondiabetic participants (+2.97 mmHg vs. +0.80 mmHg; $P = 0.06$), and in participants with eGFR <60 vs. ≥60 ml/min/1.73 m^2 (+3.42 vs. +1.07 mmHg; $P = 0.04$). Expressing associations sizes per the 1–µg/dl threshold generated similar results (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C437).

Figure 4 shows secular trends in PAF for cardiovascular and cardiac mortality and the associated NAD. From 1999–2004 to 2017–2020, PAF decreased from 7.80% (95% CI: 0.17–14.4%) to 2.50% (0.05–4.68%) for cardiovascular mortality and from 9.75% (1.92–16.5%) to 3.14% (0.61–5.39) for cardiac mortality; cardiovascular and cardiac NADs decreased from 53 878 (95% CI: 1167–99 253) to 7539 (160–14 108) and from 54 672 (10 751–92 226) to 7718 (1491–13 233).

DISCUSSION

From 1999–2004 to 2017–2020, BL decreased from 1.76 to 0.93 µg/dl and the proportion of US adults with BL <1 µg/dl increased from 19.2% to 63.0%. Given this substantial reduction in lead exposure – to our knowledge for the first time – we undertook time-stratified analyses of NHANES data covering the 1999–2019-time interval. Among 33 286 participants with available linkage with the National Death Index, total, noncardiovascular and cancer mortality were not associated with BL, whereas cardiovascular and cardiac mortality were with HRs for a fourfold BL increment amounting to 1.44 and 1.52, respectively. However, from 1999 to 2000 onwards, the HRs relating cardiovascular and cardiac mortality weakened and became nonsignificant from 2001–2002 onwards until 2007–2008. Given the wide range of cardiovascular diseases attributable to lead exposure according to the Global Burdon of Disease Investigators [18], we used cardiac rather coronary mortality as study endpoint. In the mediation analyses, the direct contribution of BL to cardiovascular and cardiac mortality was no longer significant in the 2007–2010 cycle, while the indirect contributions mediated via systolic BP or hypertension were not significant in any cycle. Among 34 806 NHANES participants with extended baseline data, a fourfold BL increment was associated with higher systolic/diastolic BP (+1.14/+0.68 mmHg) with stronger associations in high-risk groups, including Blacks, older participants, and patients with diabetes or reduced eGFR. From 1999–2004 to 2017–2020, PAF for

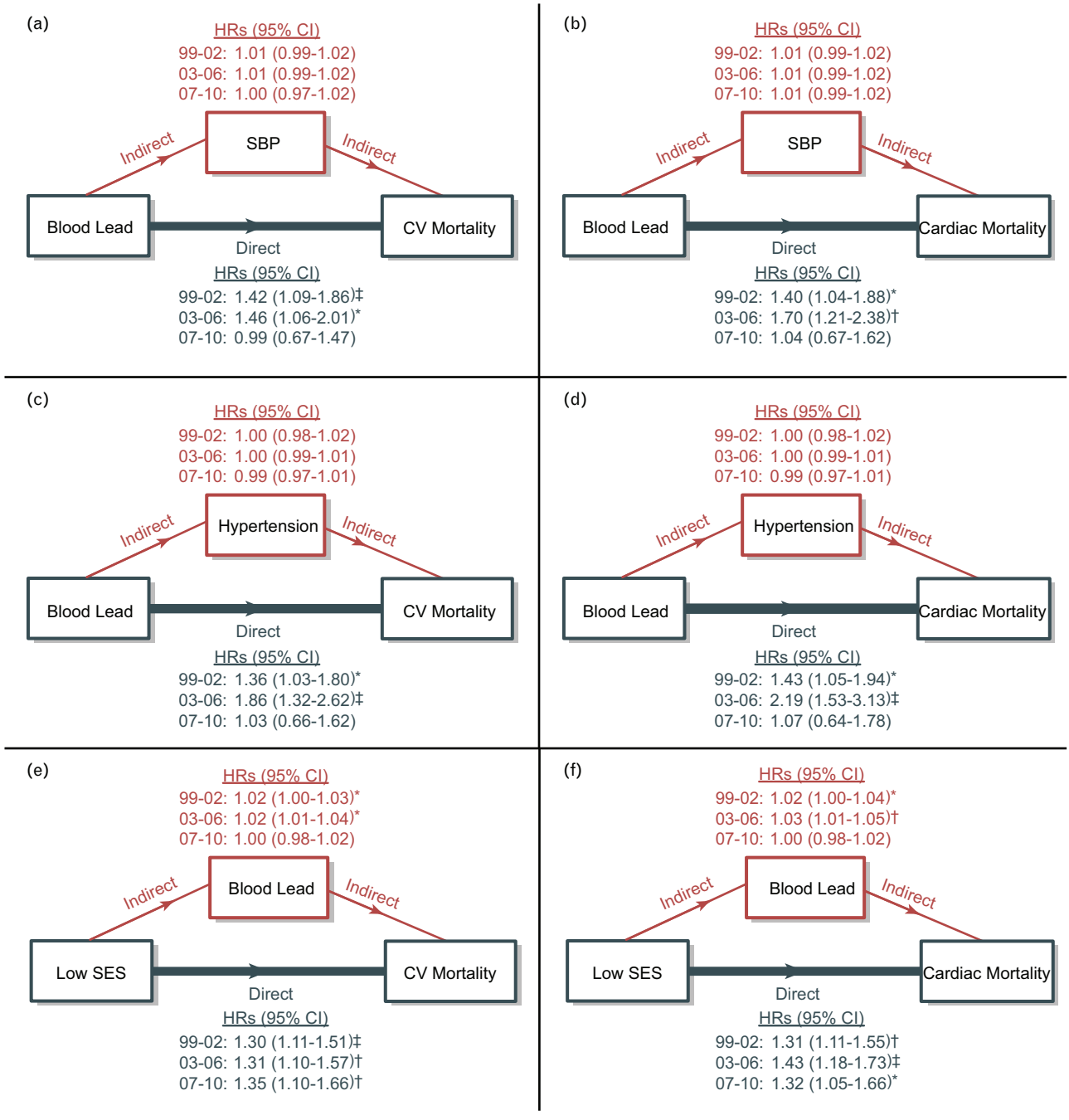

FIGURE 3 Mediation analyses. The direct and indirect contributions of systolic blood lead (SBP) to cardiovascular (a, c) and cardiac mortality (b, d) in time-stratified analyses (1999–2002; 2003–2006, and 2007–2010). The indirect contributions of blood lead running via systolic blood pressure (a, b [$P \geq 0.07$]) or hypertension (c, d [$P \geq 0.53$]) are not significant. The direct and indirect contributions of low socio-economic position (SES) to cardiovascular mortality (a) and cardiac mortality (b) in time-stratified analyses (1999–2002; 2003–2006, and 2007–2010). Low socio-economic position, defined as a poverty index of ≤1.3 and less than college education, was associated with higher BLs compared with the remainder of the study population (1999–2002: 1.97 vs. 1.65 μg/dl, 2003–2006: 1.83 vs. 1.48 μg/dl, 2007–2010: 1.51 vs. 1.29 μg/dl; P for all < 0.001). Significance of the hazard ratios (HR): $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.001$.

cardiovascular and cardiac mortality decreased over threefold to approximately 3% and the cardiovascular and cardiac NADs decreased from over 50 000 to less than 8000. An observational study cannot establish a causal relation, so that in the context of this study we used the term attributable deaths rather than preventable [7] deaths.

The observation that total, noncardiovascular and cancer mortality were not significantly associated with BL is at variance with previous NHANES publications [5–8] and an analysis of American men enrolled in the Normative Aging Study [22]. The significant association of cardiovascular mortality with BL is consistent with most NHANES reports [5–8], the Normative Aging Study [22] and a Korean cohort study [23]. According to the International Agency for Research on Cancer, there is very limited evidence for the carcinogenicity of inorganic lead in humans (group 2A) and no evidence for organic lead compounds (group 3) [24]. Residual confounding was suggested as explanation of the

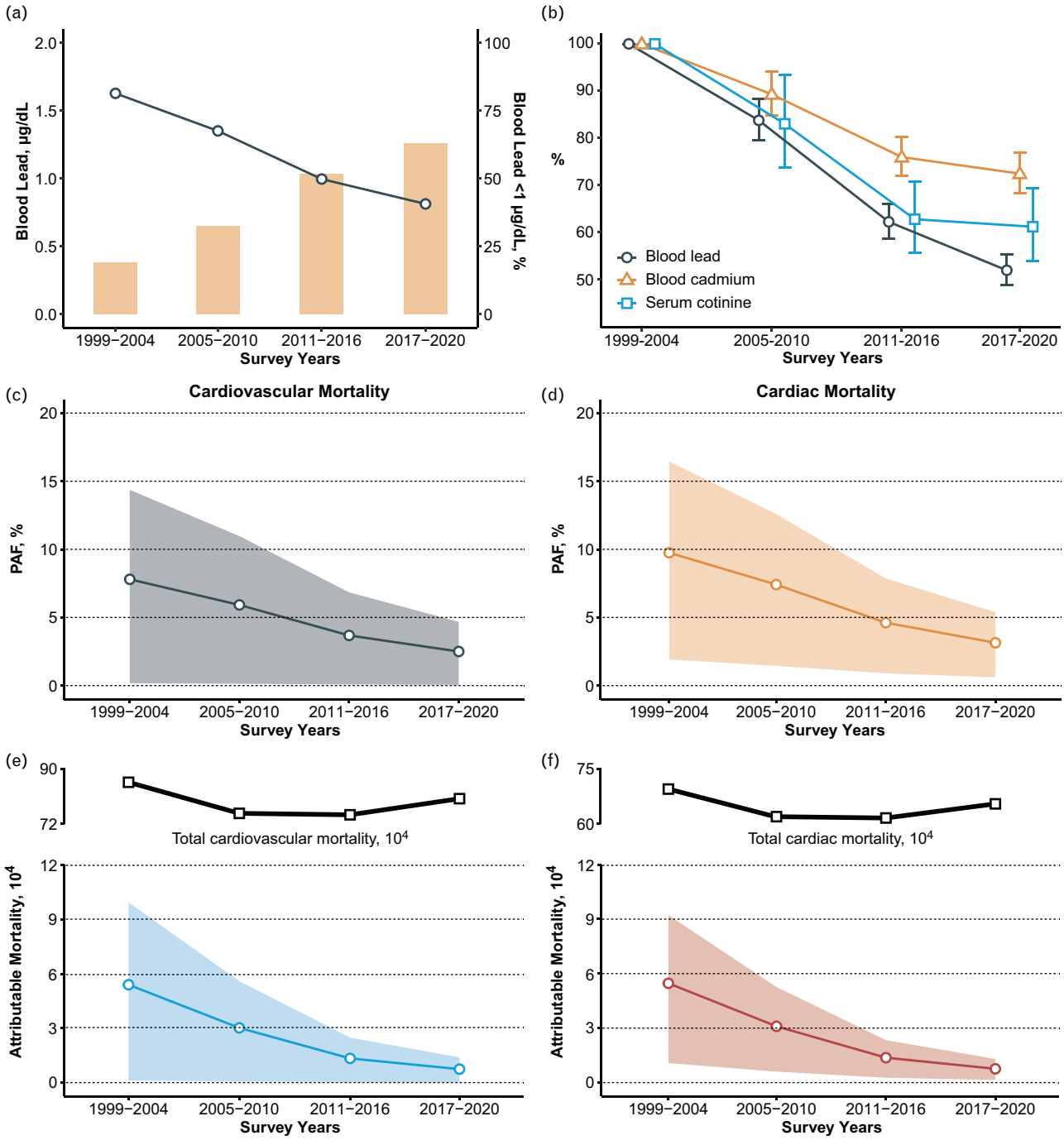

FIGURE 4 Time trends in the exposure variables and the population attributable fraction and attributable deaths for cardiovascular and cardiac mortality. Estimates are standardized to the 2020 US Census by ethnicity, sex, and 5-year age category. The panel shows the decrease in blood lead from 1999–2004 until 2017–2020 and the increase in the proportion of participants with BL lower than 1.00 µg/dl. In panel b, the percentage decrease in blood lead and cadmium and serum cotinine are depicted. Panels c–g describe the adjusted population attributable fraction (PAF) by survey period for cardiovascular mortality (c) and cardiac mortality (d) and the number of attributable cardiovascular (e) and cardiac (f) deaths for examination cycles ranging from 1999–2004 until 2017–2020. The colored areas around the lines represent the 95% confidence interval. For comparison, the annual averaged total number of cardiovascular deaths (e) and cardiac deaths (f) are given for the same survey periods. The trend in attributable cardiovascular and cardiac mortality deviates from the trend in total mortality.

association of cancer mortality with lead in NHANES II and III [25]. Accounting for the competing risks of noncardiovascular and cancer mortality did not affect the current estimates of the association between cardiovascular mortality and BL. Given the toxicokinetics of lead exposure [15,16], earlier compared with later NHANES cycles increasingly reflect the historical rather than the current environmental lead exposure, particularly in older individuals. Currently, the primary exposure route of the general population runs via respirable lead-contaminated particulate, containing lead deposited in the 20th century [15,16]. An additional confounder is that NHANES participants

enrolled in earlier NHANES cycles have a longer follow-up and therefore a higher absolute risk of death, irrespective of whether the cause is noncardiovascular (Figure S2, Supplemental Digital Content, http://links.lww.com/HJH/C437) or cardiovascular (Figure S3, Supplemental Digital Content, http://links.lww.com/HJH/C437). Life expectancy might explain why in Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C437 HRs were higher in young than old participants, in individuals with high vs. low poverty index, and in participants with eGFR $\geq$60 vs. $<$60 ml/min/1.73 m^2 [26].

Low SES was associated with higher BLs compared with the remainder of the study population and was directly associated with an increased risk of cardiovascular and cardiac mortality, while the associations running via BL lost significance in 2007–2010 cycle. These findings are in keeping with a recent NHANES report [27], in which unemployment, lower family income, food insecurity, less than high school education, no private health insurance, and not being married were significantly and independently associated with premature death before 75 years of age. Adjusting for these social determinants reduced the HR for premature mortality in Blacks compared with Whites from 1.59 (95% CI: 1.44–1.76) to 1.00 (95% CI: 0.91–1.10), suggesting complete mediation of the racial disparity difference in mortality [27]. Of interest, in a Mendelian randomization study using data from CARDIoGRAPMplusC4D 1000 Genomes and the UK Biobank SOFT CAD databases, genetically instrumented BL was not associated with systolic or diastolic BP or coronary heart disease, suggesting that the epidemiologically observed associations between mortality and BL are not causal [28]. Social inequalities in the access to healthcare [27,29] might also explain why since 2011 the standardized mortality rates for cardiovascular mortality and of all of its components levelled off in the US [30].

The time-stratified strategy sets our study apart from most, if not all, previous NHANES analyses [5–8]. One publication reported parallel decreasing trends in the BL, BCd and cardiovascular mortality from 1988–1994 to 1999–2004, but did not engage in a true time-stratified analysis [8]. Our study has addressed some emerging issues in population health metrics [31], including the inflation of the relative risk based on outdated blood lead levels, not differentiating relative from absolute risk, clustering of risk factors and exposures within individuals, and disregarding noncardiovascular disease. Nevertheless, our current results must also be interpreted within the context of potential limitations. First, too few deaths precluded robust analyses of cardiovascular and cardiac mortality from 2009 to 2010 onwards. Second, using mortality endpoints disregards the huge progress made in the treatment of vascular disease, which makes many patients survive cardiovascular accidents that were fatal in the 20th century. Mortality endpoints therefore underestimate the true incidence of cardiovascular disease. Third, residual confounding remains a potential limitation due to unmeasured variables. Fourth, the impact of immigration was not comprehensively addressed due to small proportion of immigrants (10%) in the study population. Fifth, the findings of this study may be applicable to developed regions such as the European Union, where repeated BL measurement in the same population showed declining trend over 20 years (Figure S4, Supplemental Digital Content, http://links.lww.com/HJH/C437) [14]. However, their generalizability to continents like Asia, characterized by diverse developmental statuses, may be limited. Finally, although we kept BCd as a covariable, we cannot exclude co-exposure to other heavy metals or environmental pollutants.

What are the implications of our study for addressing lead exposure in the US? Further reducing the adverse health effects of environmental lead exposure should remain a priority, but will require revision of public health policies, particularly diminishing the exposure to $PM_{2.5}$ [15,16]. This includes not only reducing emissions, but also empowering subpopulations with low SES. An analysis of Medicare data covering 623 million-person years from 73 million individuals aged 65 years or older followed from 2000 through 2016 estimated associations between mortality and annual PM2.5 [32]. The analyses were stratified for Black vs. White ethnicity and income level (Medicaid eligible vs. ineligible). Lower $PM_{2.5}$ exposure was associated with lower mortality in the full population, but marginalized subpopulations, including high-income blacks, low-income whites and low-income blacks, appeared to benefit more as $PM_{2.5}$ levels decreased compared with high-income whites [32]. Obvious routes of lead exposure need to be addressed, such as replacing lead pipes for the distribution of drinking water in some US states, the promotion of lead-free alternatives for ammunition, and phasing out leaded aviation fuel [33]. Other more difficult to investigate sources of lead exposure must be addressed as well, such as the use of recreational or illicit drugs, affecting 21.9% of American aged 12 years or older [34].

CONCLUSION

Our time-stratified analysis highlights the huge progress made over the past decades in containing environmental lead exposure and the associated adverse health effects by imposing and reinforcing strict environmental policies in the United States and worldwide. The public health implications of our observations, combined with the contemporary literature [27,32], in our view are straightforward. Along with eliminating the few remaining point sources of lead, some of which until now escaped detection, lead-exposure containing environmental policies should focus on reducing $PM_{2.5}$ exposure [15,16,32], and on empowering deprived social groups in risk factor recognition, management of their multimorbidity [35], and by facilitating their access to healthcare [27,32].

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Conflicts of interest

There are no conflicts of interest.

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