Associations between blood lead and urinary cadmium concentrations and all-cause and specific causes of mortality: estimating intervention effects using the parametric g-formula

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Abstract

Objective

Previous studies in the US reported a high mortality risk associated with higher blood lead levels (BLLs) and urinary cadmium (UCd) levels. The aim of this study was to extend the follow-up of the previous analyses and use the parametric g-formula to estimate the 27-year risk of all-cause and specific causes of mortality.

Methods

We used data on 14,311 adults aged ≥ 20 years enrolled in the NHANES-III between 1988 and 1994 and followed up through Dec 31, 2015. Time and cause of death were determined from the National Death Index records. We used the parametric g-formula with pooled logistic regression models to estimate the relative and absolute risk of all-cause, cardiovascular, and cancer mortality under different potential threshold interventions on BPb and UCd concentrations.

Results

Median follow-up was 22.5 years, 5,167 (36%) participants died by the end of the study; 1,550 from cardiovascular disease and 1,135 from cancer. An increase of BLLs and creatinine corrected UCd from the 5th (0.70 µg/dL and 0.04 µg/g for BLLs and UCd) to the 95th percentile (9.70 µg/dL and 1.63 µg/g for BLLs and UCd) was associated with an increased risk of all-cause by 138% (95% CI, 14 to 196) and a 126% (95% CI, 77 to 383). BLLs and UCd were associated with an increase of 109% (95% CI, 4 to 268) and 37% (95% CI, -0.20 to 239) in the risk of cardiovascular mortality when comparing the 5th to the 95th percentiles of exposure. The corresponding increase in risk for cancer mortality was 287% (95% CI, 12 to 691) and 144% (95% CI, -0.34 to 281) for BLLs and UCd, respectively. We found higher risk differences among men and older participants as compared to their counterparts.

Conclusion

Interventions to reduce historical exposures to lead and cadmium could have prevented several deaths, especially among individuals ≥ 50 years of age as well as in men.

Introduction

Cardiovascular disease and cancer are the two leading causes of death, accounting for 17.9 million and 9 million deaths worldwide, respectively, in 2016 (1). While there is a marked decline in cardiovascular diseases mortality rates, cancer mortality is increasing and is even the leading cause of death in many countries (2). In 2021, it was estimated that 608,570 Americans will die from cancer, corresponding to

more than 1600 deaths per day (3). These two causes of death, while seemingly different, more data reveal common risk factors including being overweight or obese (4, 5), not being physically active (6, 7), having a poor diet (8), and exposure to environmental chemicals such as lead and cadmium (9).

Lead and cadmium are among the most common environmental and occupational pollutants derived from natural resources or as a byproduct from industries such as mining. In the last decades, lead and cadmium exposures have declined sharply in the United States (9, 10); however, in 2019 the US Agency for Toxic Substances and Disease Registry ranked lead and cadmium second and seventh on the National Priorities List of substances that pose the most significant potential threat to human health (11).

While epidemiological studies have consistently reported that exposures to lead and cadmium above the safety standards were associated with increased risks of cardiovascular, cancer, and all-cause mortality (12, 13); studies also reported that chronic low-concentration lead exposures (between 1–5 µg/dL in the blood) may increase the risk of premature death, especially from cardiovascular diseases (14, 15). In contrast, there were conflicted results for cancer mortality risk at these ranges of exposure (15). Few epidemiological studies have examined prospectively the association of low-concentration cadmium exposure in relation to the risk of cancer and cardiovascular disease mortality. Results on urinary cadmium concentrations and mortality have been reviewed by Larsson et al. in a recent meta-analysis which highlighted the limited number of prospective studies (n = 9 studies) and conflicted results; and concluded for a need of further large prospective studies (16). Major limitations persist when analyzing the prospective associations of lead and cadmium with mortality outcomes. First, the non-adjustment for dietary intake (one of the main sources of exposure) and predictor of cancer and cardiovascular disease mortality. Second, the non-consideration of mutual adjustment between these two metals that could confound each other. Third, all previous prospective studies used a Cox proportional hazard model to estimate hazard ratios, potentially violating proportional hazards assumption since the risk of mortality in relation to the exposure to these metals may vary over time. Finally, previous studies focused on the consequences of exposure to these metals, when it is also important to model the population level impact of potential policies or interventions on reducing exposure levels for informing public health. The hazard ratio alone does not provide this information as the clinical significance depends on the baseline rate (17). It is therefore necessary to address all these limitations and to consider the use of models that allow us to overcome proportional hazards assumption and to evaluate the impact of potential interventions on these exposures.

We, therefore aimed first, to extend the follow-up of the previous studies in the US National Health and Nutrition Examination Survey (NHANES-III). Second to use a pooled logistic regression (a model for the discrete-time hazard) within the parametric g-formula to address previous limitations while flexibly simulating the expected all-cause and specific causes of mortality distributions for hypothetical interventions related to lead and cadmium exposures in the US population.

Methods

Design and participants

We used data from the US National Health and Nutrition Examination Survey (NHANES). The NHANES is an ongoing survey conducted by the Centers for Disease Control (CDC) and Prevention that uses a representative sample of non-institutionalized civilians in the US; selected by a complex, multistage, stratified, clustered probability design. Information on participants was collected by interviews and in personal physical examinations. The interview includes background information such as socio-demographic, dietary and health-related questions. The examination component consists of medical and physiological measurements, as well as laboratory tests. The National Center for Health Statistics Ethics Review Board approved all NHANES protocols, and all survey participants completed a consent form. The detailed protocol on NHANES methodology and data collection is available on https://www.cdc.gov/nchs/nhanes/index.htm. For this study, we initially included adults aged ≥20 years enrolled in the NHANES-III between 1988 and 1994, with data on blood lead and urinary cadmium concentrations (n = 16,040). Exposure and covariate data from NHANES-III were then linked to the National Death Index mortality data.

Mortality data

A full description of mortality linkage methods is available from the National Center for Health Statistics (NCHS) (18). Briefly, the de-identified and anonymized data of the NHANES III participants were linked to National Death Index mortality files based on 12 identifiers for each participant (eg, Social Security number, sex, and date of birth) with a probabilistic matching algorithm to determine mortality status. The NCHS public-use linked mortality file provides mortality follow-up data from the date of NHANES III survey participation until December 31, 2015 (1988–2015). Participants with no matched death record at this date were assumed alive during the entire follow-up period. 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 were recorded in the public-use linked mortality files using the following ICD-10 codes: Cardiovascular diseases including heart diseases (I00-I09, I11, I13, I20-I51) and cerebrovascular diseases (I60-I69) and malignant neoplasms (C00-C97). From the 16,040 participants with baseline data, 1,729 had missing data on mortality and other covariates. The final study sample included 14,311.

Measurements of blood lead and urinary cadmium

Blood and urine samples were collected during the medical examination. The laboratory methods for the processing of these samples are described in detail elsewhere (20). Briefly, the blood and urine specimens were frozen (−30°C and −20°C; respectively), stored, and shipped for analysis to the Division of Laboratory Sciences, National Center for Environmental Health at the Centers for Disease Control and Prevention in Atlanta, Georgia (USA). Lead (µg/dL) concentration was measured in whole blood using inductively coupled plasma mass spectrometry. Urinary cadmium was measured by graphite furnace atomic absorption with Zeeman background correction using the CDC and Prevention modification (20) of the method proposed by Pruszkowska et al. (21). Specimens were analyzed in duplicate, and the

average of the two measurements was reported. The detection limit were 1.0 µg/dL (0.048 µmol/L) and 0.03 µg/L for the blood lead and the urinary cadmium; respectively. For study participants who had concentrations of blood lead below the level of detection (n= 1217; 8.5%), values were imputed using LOD/$\sqrt{2}$ [0.7 µg/dL]. Urinary creatinine measured using the Jaffe reaction with a Beckman Synchron AS/ASTRA Clinical Analyzer (Beckman Instruments, Inc., Brea, CA), was used to account for urine dilution.

Covariates

Baseline covariates were collected when individuals participated in a household interview and demographic information—including sex (male/female), age (continuous; years), ethnicity (Mexican-American, other Hispanic, not Hispanic), poverty to income ratio (categorized in tertiles), the number of years of education attended and completed (continuous; years), area of residence (metro and non-metro counties), and smoking status (current, former and never) was obtained. Information on body-mass index ([BMI] continuous; kg/m^2), physical activity (None, One to 14 times, 15 or more times; per month) and overall dietary quality indexes (continuous) was obtained during the medical examination. Dietary intake was collected using a 24-hour dietary recall. We derived the diet quality indexes as measured by the Healthy Eating Index 2015 (HEI-2015) (22) and the adapted dietary inflammatory index (23), from the daily intakes of foods/beverages, energy, and nutrients of the 24-hour dietary recall. A complete description of the development of these scores is described in **Supplementary Methods**.

Statistical analysis

Complete data on exposures, covariates, and mortality were available for 14,311 participants. We log-transformed (base 2) Blood lead and urinary cadmium concentrations to reduce the influence of outliers and descriptive and bivariate analyses are reported as geometric means and geometric standard errors (SE) by population characteristics. We used the parametric g-computation to estimate risk ratios (RR) and risk differences (RD) of all-cause and specific causes of mortality under hypothetical interventions. In 1986, Robins introduced the g-methods, a class of causal inference techniques that allows building outcome prediction model based on observed quantities, and then predicts potential outcomes under potential hypothetical intervention (24, 25). In recent years, there have been substantial advances in the application of this method, and have been used for instance to evaluate hypothetical interventions on sources of lead exposure on BLLs (26). The parametric g-formula is a generalization of the standardization method and allows to flexibly simulate and estimate survival curves to visualize time-specific effect estimates of any form of hypothetical intervention. A more detailed discussion of this method is presented elsewhere (27, 28). Briefly, we first fitted a pooled logistic regression conditional on covariates and follow-up time, after arranging the data into a person-time structure. The discrete-times hazards of all-cause and specific causes of mortality for each 2-fold increase in the baseline metals concentrations (log_2-transformed to reduce skewness) were then estimated. This estimated risk was used to predict the mortality under two hypothetical interventions specifying thresholds for metals concentrations. We then compared the estimated risk of mortality under the intervention 1: had all participants were assigned a high concentration (e.g. the 95^{th} percentiles values of the metals

distributions) with the estimated risk of mortality under the intervention 2: had all participants were assigned a low concentration (e.g. the 5^{th} percentiles values of the metals distributions). This approach assumed a linear association between metals concentration and death; to check the assumption, we then used multivariable restricted cubic splines with three knots placed at the 10th, 50th, and 90th percentiles of each metal concentrations distribution to provide a graphical presentation (29). Splines allowed us to test whether there was any departure from linearity.

Finally, we also considered interventions comparing quartile groups of lead and cadmium concentrations. We categorized metal concentrations into quartiles and estimated the discrete-times hazards of all-cause and specific causes of mortality for each quartile with the first quartile group, the lowest metal concentration, as the reference category. We then compared the estimated risk of mortality under the intervention 1: had all participants belonged to the bottom quartile group with the estimated risk of mortality under the intervention 2: had all participants belonged to the low quartile group.

There is no know safety levels for the blood and urinary concentrations of these metals in adults. We therefore chose the interventions listed above based on previous epidemiologic analyses, as discussed elsewhere (14). Models were adjusted for age, sex, ethnicity, poverty index, educational level, area of residence, smoking status, BMI, physical activity, diet quality evaluated by the healthy eating index and metals concentrations (mutual adjustment). The selection of potential confounders was done a priori. We also included product terms between the metals concentrations and time in all models to account for the time-varying risk. All analyses were weighted by the provided sample weights to account for the unequal probabilities of inclusion and response rates. We estimated 95% confidence intervals (CIs) of the RR and the RD using non-parametric bootstrap (M=200) and used the 2.5th and 97.5th percentiles as the lower and upper confidence interval limits, respectively samples.

We additionally investigated age (< 50 years and ≥ 50 years)- and sex-specific estimates in stratified analyses as previous studies reported potential effect modification of the associations between metals concentrations and mortality by sex and age (12, 14). We also evaluated effect modification by age and sex using Cochran Q tests.

Sensitivity Analyses

We ran sensitivity analyses by performing unweighted models that not account for the NHANES survey unequal probabilities of inclusion and response rates because the weighted method is inefficient analysis due to the large variability in assigned weights (30). The unweighted analysis yields correct estimates when models are adjusted for the auxiliary variables used to define the weights (i.e., age, sex, and ethnicity) (30).

Statistical analyses were performed using R version 4.0.4 and the Statistical Analysis System software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 14,311 participants were included (mean age 48.0 ± 18.1) for this analysis.. The blood lead concentrations ranged from 0.70 µg/dL to 56.0 µg/dL (0.034 µmol/L to 2.70 µmol/L), with a geometric mean (GM) of 2.97 µg/dL (geometric standard error [GSE]= 0.02). BLLs were higher in older, male, and current and former smoker participants, and in participants that reported drinking alcohol more than four time per month, and those who are in the categories of less healthy dietary indices and low poverty to income ratio (table 1). The urinary creatinine standardized cadmium concentrations ranged from 0.002 µg/g to 23.35 µg/g, with a GM of 0.36 µg/g (GSE = 0.003). Participants who had the highest concentrations of urinary cadmium were older, and more likely to be female, to be current and former smokers, and to not practice physical activity. There were no major differences for other participant characteristics (table 1).

Blood lead and urinary cadmium concentrations and all-cause and cause-specific mortality

During a median follow-up of 22.5 years (IQR 16.3–24.7), 5,167 (36%) participants died with 1,550 (30%) and 1,135 (22%) attributable to cardiovascular disease and cancer, respectively.

When comparing a potential intervention assigning all participants to the 5th percentile value (0.70 µg/dL and 0.04 µg/g for lead and cadmium; respectively), to all participants to the 95th percentile value (9.70 µg/dL and 1.63 µg/g for lead and cadmium; respectively), we observed a 138% (95% CI, 14 to 196) and a 126% (95% CI, 77 to 383) increased risk of all-cause mortality at 27 years of follow-up, for blood lead and urinary cadmium, respectively. On the absolute scale, we observed 4.17% (95% CI, 1.54 to 8.77) and 6.22% (95% CI, 4.51 to 12.00) increases in all-cause mortality associated with blood lead and urinary cadmium, respectively (Figure 1, Table 2).

For cause-specific mortality, comparing the 5th to the 95th percentiles assignments, blood lead and urinary cadmium showed a 109% (95% CI, 4 to 268) and a 37% (95% CI, -0.20 to 239) increased risk of cardiovascular mortality at 27 years of follow-up, corresponding to a percentage risk difference of 1.52% (95% CI, 0.09 to 3.74) and 1.06% (95% CI, -0.57 to 3.50) for blood lead and urinary cadmium, respectively (Figure 1, Table 2). The estimated 27-years cancer mortality risk after intervening to set all participants to the 95th percentile compared to the 5th percentile was increased by 287% (95% CI, 12 to 691) and 144% (95% CI, -0.34 to 281) for blood lead and urinary cadmium, respectively; yielding a percentage risk difference of 1.32% (95% CI, -0.09 to 3.67) and 0.64% (95% CI, -0.98 to 2.80) for blood lead and urinary cadmium, respectively (Figure 1, Table 2). We did not observe any departure from linearity in the associations between metals concentrations and mortality when using smoothing splines (Supplemental Material; Figure S1).

When we considered interventions comparing quartile groups of lead and cadmium, the estimated RD of 27-years all-cause mortality after intervening to set all participants to the quartile 4 of metals concentrations compared to setting all participants to the quartile 1 showed the percentage points increase of 5.52% (95% CI, 1.25 to 18.25) and 10.48% (95% CI, 5.15 to 27.99) for blood lead and urinary cadmium, respectively (Figure 2, Table 3). The corresponding 27-years RD for cardiovascular mortality

was 5.18% (95% CI, 0.47 to 48.61) and 6.31% (95% CI, 3.76 to 50.38) for blood lead and urinary cadmium, respectively; and for cancer mortality 4.17% (95% CI, -0.28 to 26.00) and 0.13% (95% CI, -1.57 to 48.35) for blood lead and urinary cadmium (Figure 2, Table 3).

Analyses stratified by sex and age

We found that the associations between the blood lead concentration and all-cause (p-heterogeneity = 0.021) and cardiovascular mortality (p-heterogeneity < 0.001) were more pronounced for older (≥ 50 years) compared to younger (< 50 years) participants, while for cancer mortality, the association was similar for younger and older participants (p-heterogeneity = 0.429) (Supplemental Figure 2 and Table 1). The associations between the urinary cadmium concentration and all-cause (p-heterogeneity = 0.020), cardiovascular (p-heterogeneity = 0.093) were more pronounced for older (≥ 50 years) compared to younger (< 50 years) participants, while for cancer mortality, the association was similar for younger and older participants (p-heterogeneity = 0.525) (Supplemental Figure 2 and Table 1). Analyses stratified by sex showed that the associations between urinary cadmium concentrations and mortality were more pronounced in men (p-heterogeneity < 0.10). There was no difference mortality risk associated to blood lead (p-heterogeneity > 0.10) (Supplemental Figure 3 and Table 2).

Sensitivity Analyses

When the models were unweighted, we observed the same pattern of associations for all-causes and cancer mortality both for lead and cadmium exposures (supplemental Table 3). However, the association between blood lead concentration and cardiovascular mortality were more pronounced with a RR of 2.09 (95% CI, 1.04 to 3.68) at 27 years of follow-up compared to the model without the survey weights (RR = 1.02 (0.52 to 2.80), corresponding to a percentage point increase of 0.69% (95% CI, -2.72 to 3.85) (supplemental Table 3).

Discussion

Using a large nationally representative sample of US adults, we found that those with high concentrations of blood lead and urinary cadmium showed an 27 years increased risk of all-cause mortality (about 6,460,092 and 9,635,916 deaths, respectively), cardiovascular disease mortality (about 2,354,758 and 1,642,134 deaths, respectively) and cancer mortality (about 2,044,921 and 991,477 deaths, respectively) compared with those with low concentrations. The associations were more pronounced for older participants, except for cancer mortality associated to blood lead. In addition, all these associations were more pronounced in men than women for urinary cadmium.

Our findings are in line with previous population-based studies showing that exposure to lead and cadmium was associated with increased risks of cardiovascular, cancer, and all-cause mortality (12–16). Two studies reported that chronic low concentrations of lead exposure was associated with premature death, especially from cardiovascular disease (14, 15). In contrast, there was no association for cancer mortality risk (15). Several epidemiological studies have examined prospectively the associations of

cadmium exposure in relation to the risk of all-causes (12, 31–36), cancer (32, 37–39) and cardiovascular disease mortality (12, 32–34, 37). Most studies have reported a positive association between urinary cadmium concentrations and mortality, except one study for cardiovascular (12), two studies for cancer (32, 37) and all-causes mortality (12, 31). In comparison to other studies, our study explored the potential effect on mortality of different theoretical interventions on exposure levels of these metals.

Environmental exposure to lead occurs continuously over a lifetime and lead is retained in the body for decades. Blood lead is an established biomarker of recent exposure, although it also shows a small component with a half-life of 5–20 years that reflects endogenous exposure from bone lead redistribution (40). Several mechanisms have been proposed for the role of lead in cardiovascular events. Lead exposure can result in oxidative stress and inflammation, diminishes endothelium relaxation, and promotes development of atherosclerosis and thrombosis (41). In addition, lead is a well-known risk factor for hypertension and has been associated with peripheral arterial disease, electrocardiographic abnormalities, left-ventricular hypertrophy, alteration of cardiac conduction, cardiac disease, and thus increased mortality due to cardiovascular disease (40, 42). Regarding cancer toxicity, the mechanisms by which lead may lead to tumor is unclear. However, lead has been defined as a “probable human carcinogen” by the International Agency for Research on Cancer (43). It has been proposed that lead can facilitate the process of carcinogenesis by inhibiting DNA synthesis and repair and by interacting with binding proteins, hindering tumor suppressor proteins (44). Lead may also affect carcinogenesis through mechanisms involving oxidative damage, induction of apoptosis, and altered signaling pathways (45).

While Blood cadmium tends to reflect recent exposures, urinary cadmium reflects kidney cadmium contents and, with a half-life of 15–30 years, is an established biomarker of cumulative body burden. The cardiovascular toxic effects of cadmium exposure have been well described. Experimental evidence supports a role for cadmium in atherosclerosis, including increased inflammation (46) and endothelial oxidative stress(47, 48). Results from epidemiological studies show that a high cadmium exposure is associated with hypertension (49), the growth of atherosclerotic plaques (50, 51) and cardiovascular disease (52–54). Evidence for cancer toxicity stems from various mechanisms. Cadmium may promote carcinogenesis through induction of oxidative stress (55, 56), suppression of DNA, changes in DNA methylation and apoptosis repair (56–58). Another alternative hypothesis is through estrogenic activities (59).

This study used the NHANES III dataset, a large, national survey whose findings are generalizable to the U.S. adult non-institutionalized population. Although there are strengths to this study including its large sample-size and random sampling, the mutual adjustment between lead and cadmium metals, the adjustment for dietary intake (one of the main source of exposure) and, most importantly, we used a method that was not based on the proportional hazard assumptions and the graphic representation of the risk at each follow-up time allow us to show that the risk varies over the duration of the follow-up. For example, the risk difference for cardiovascular mortality associated with blood lead and urinary cadmium concentration were + 1.52% and + 1.06%, at the end of the follow-up and + 0.47% and + 0.27% at the mid-

follow-up (13 year) (supplemental Tables 4 and 5). There are important limitations to note. The key limitation is that for lead we relied on blood concentrations, therefore the cumulative chronic or long-term exposure was not accounted for. Urine measurement are better indicators of cumulative exposure and would have strengthened the results on lead exposure. In addition, covariables data were only available at baseline. Thus, the exposure-confounders relationships were not well defined temporally. Another limitation is that we relied on death certificates for the underlying cause of death, but they are imperfect (60). Most importantly, although the main potential confounding factors were accounted for, there could be residual confounding due to other genetic and environmental factors that were either not measured or measured inadequately, that may have influenced our findings. Finally, because internal dose metrics cannot define correctly the complete history of exposure and duration, the timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

This study focused only on hypothetical interventions related to lead and cadmium exposures to simulate what would have been the benefits of historical interventions. We recommend that future directions in environmental health research explore other interventions based on, for example, dietary and lifestyle factors, which may be complementary to the pollutant-based interventions.

In conclusion, our findings suggest that blood lead and urinary cadmium are associated with all-cause, cardiovascular and cancer mortality. Despite the continuous decrease in lead and cadmium exposures in the U.S. population, we confirmed the previously reported associations and showed that several deaths could have been prevented under intervention to reduce the blood lead concentration from 9.70 µg/dL to 0.70 µg/dL and the creatine corrected urinary cadmium from 1.63 µg/g to 0.04 µg/g, respectively. Intervening to reduce historical exposures to these metals would be more effective (on the absolute scale) among individuals ≥ 50 years of age as well as in men.

Declarations

Conflict of Interest and Authorship Confirmation

- All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.
- This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.
- The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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Tables

Table 1: Blood lead and urinary cadmium geometric means and standard errors by study population baseline characteristics

		Blood lead (µg/dL)	Urinary cadmium (µg/g)
	N (%)	GM (GSE)	GM (GSE)
Age classes (years)			
< 50	8,170 (57.09)	2.59 (0.0)	0.26 (0.0)
≥ 50	6,141 (42.91)	3.56 (0.0)	0.56 (0.0)
Sex			
Women	7,570 (52.90)	2.26 (0.0)	0.42 (0.0)
Men	6,741 (47.10)	4.03 (0.0)	0.31 (0.0)
Ethnicity			
Mexican-American	3,891 (27.19)	2.99 (0.0)	0.31 (0.0)
Other Hispanic	369 (2.58)	2.88 (0.1)	0.32 (0.0)
Not Hispanic	10,051 (70.23)	2.96 (0.0)	0.39 (0.0)
Smoking status			
Never smoker	6,807 (47.7)	2.37 (0.0)	0.27 (0.0)
Current smoker	4,477 (31.28)	3.86 (0.0)	0.48 (0.0)
Former smoker	3,027 (21.15)	3.32 (0.0)	0.46 (0.0)
Body-mass index			
Normal weight (<25·0 kg/m^2)	5,707 (39.88)	2.91 (0.0)	0.34 (0.0)
Overweight (25·0–29·9 kg/m^2)	4,855 (33.92)	3.18 (0.0)	0.38 (0.0)
Obese (≥30·0 kg/m^2)	3,749 (26.20)	2.80 (0.0)	0.38 (0.0)
Physical activity (per month)			
None	2,939 (20.54)	3.14 (0.0)	0.44 (0.0)
One to 14 times	5,099 (35.63)	2.89 (0.0)	0.37 (0.0)
15 or more times	6,273 (43.83)	2.95 (0.0)	0.32 (0.0)
Poverty to income ratio tertile			
First	4,776 (33.37)	3.21 (0.0)	0.38 (0.0)
Second	4,765 (33.30)	2.85 (0.0)	0.36 (0.0)
Third	4,770 (33.33)	2.85 (0.0)	0.35 (0.0)
Alcohol intake (drinks per month)			
Four or fewer	9,940 (69.46)	2.72 (0.0)	0.38 (0.0)
More than four	4,371 (30.54)	3.63 (0.0)	0.33 (0.0)
Healthy eating index tertile			
First	4,765 (33.30)	3.23 (0.0)	0.36 (0.00)
Second	4,774 (33.36)	2.91 (0.0)	0.35 (0.0)
Third	4,772 (33.34)	2.78 (0.0)	0.38 (0.0)
Adapted dietary inflammatory index tertile			
First	4,770 (0.33)	2.79 (0.0)	0.34 (0.0)
Second	4,771 (0.33)	2.95 (0.0)	0.35 (0.0)
Third	4,770 (0.33)	3.17 (0.0)	0.40 (0.0)

GM: geometric mean, GSE: geometric standard errors

Table 2: Adjusted all-cause and specific-cause of mortality risk ratio and risk difference of metals percentile 95 and 5 values using parametric g-formula with pooled logistic regression models[a]

Outcomes	Blood lead	Urinary cadmium
All-cause mortality		
Number of events (%) among low level	177/1217 (14.5%)	122/682 (17.9%)
Number of events (%) among high level	4767/13603 (35.0%)	4645/13598 (34.2%)
Adjusted risk ratio (95% CI)	2.38 (1.14 to 2.96)	2.26 (1.77 to 4.83)
Adjusted risk difference (95% CI)	+4.17% (1.54 to 8.77)	+6.22% (4.51 to 12.00)
Cardiovascular mortality		
Number of events (%) among low level	35/1217 (2.9%)	30/682 (4.4%)
Number of events (%) among high level	1423/13603 (10.5%)	1405/13598 (10.3%)
Adjusted risk ratio (95% CI)	2.09 (1.04 to 3.68)	1.37 (0.80 to 3.39)
Adjusted risk difference (95% CI)	+1.52% (0.09 to 3.74)	+1.06% (-0.57 to 3.50)
Cancer mortality		
Number of events (%) among low level	49/1217 (4.0%)	22/682 (3.2%)
Number of events (%) among high level	1027/13603 (7.6%)	1007/13598 (7.4%)
Adjusted risk ratio (95% CI)	3.87 (1.12 to 7.91)	2.44 (0.66 to 3.81)
Adjusted risk difference (95% CI)	+1.32% (-0.09 to 3.67)	+0.64% (-0.98 to 2.80)

[a]200 iterations were performed for bootstrapping the estimates 95% confidence interval

low level: 5th percentiles of blood lead (0.70 µg/dL or 0.03 umol/L) and urinary cadmium (0.04 µg/g) distributions

high level: 95th percentiles of blood lead (9.70 µg/dL or 0.47 umol/L) and urinary cadmium (1.63 µg/g) distributions

Table 3: Adjusted all-cause and specific-cause of mortality risk ratio and risk difference of metals extreme quartiles using parametric g-formula with pooled logistic regression models[a]

Outcomes	Blood lead	Urinary cadmium
All-cause mortality		
Number of events (%) among quartile 1	695/3640 (19.1%)	504/3578 (14.1%)
Number of events (%) among quartile 4	1877/3564 (52.7%)	2157/3578 (60.3%)
Adjusted risk ratio (95% CI)	1.61 (1.12 to 3.34)	2.09 (1.75 to 5.42)
Adjusted risk difference (95% CI)	+5.52% (1.25 to 18.25)	+10.48% (5.15 to 27.99)
Cardiovascular mortality		
Number of events (%) among quartile 1	168/3640 (4.6%)	123/3578 (3.4%)
Number of events (%) among quartile 4	589/3564 (16.5%)	631/3578 (17.6%)
Adjusted risk ratio (95% CI)	3.38 (1.29 to 25.66)	7.18 (3.12 to 78.03)
Adjusted risk difference (95% CI)	+5.18% (0.47 to 48.61)	+6.31% (3.76 to 50.38)
Cancer mortality		
Number of events (%) among quartile 1	172/3640 (4.7%)	98/3578 (2.7%)
Number of events (%) among quartile 4	431/3564 (12.1%)	544/3578 (15.2%)
Adjusted risk ratio (95% CI)	2.44 (1.01 to 13.48)	2.08 (0.42 to 40.73)
Adjusted risk difference (95% CI)	+4.17% (-0.28 to 26.00)	+0.13% (-1.57 to 48.35)

[a]200 iterations were performed for bootstrapping the estimates 95% confidence interval

Figures

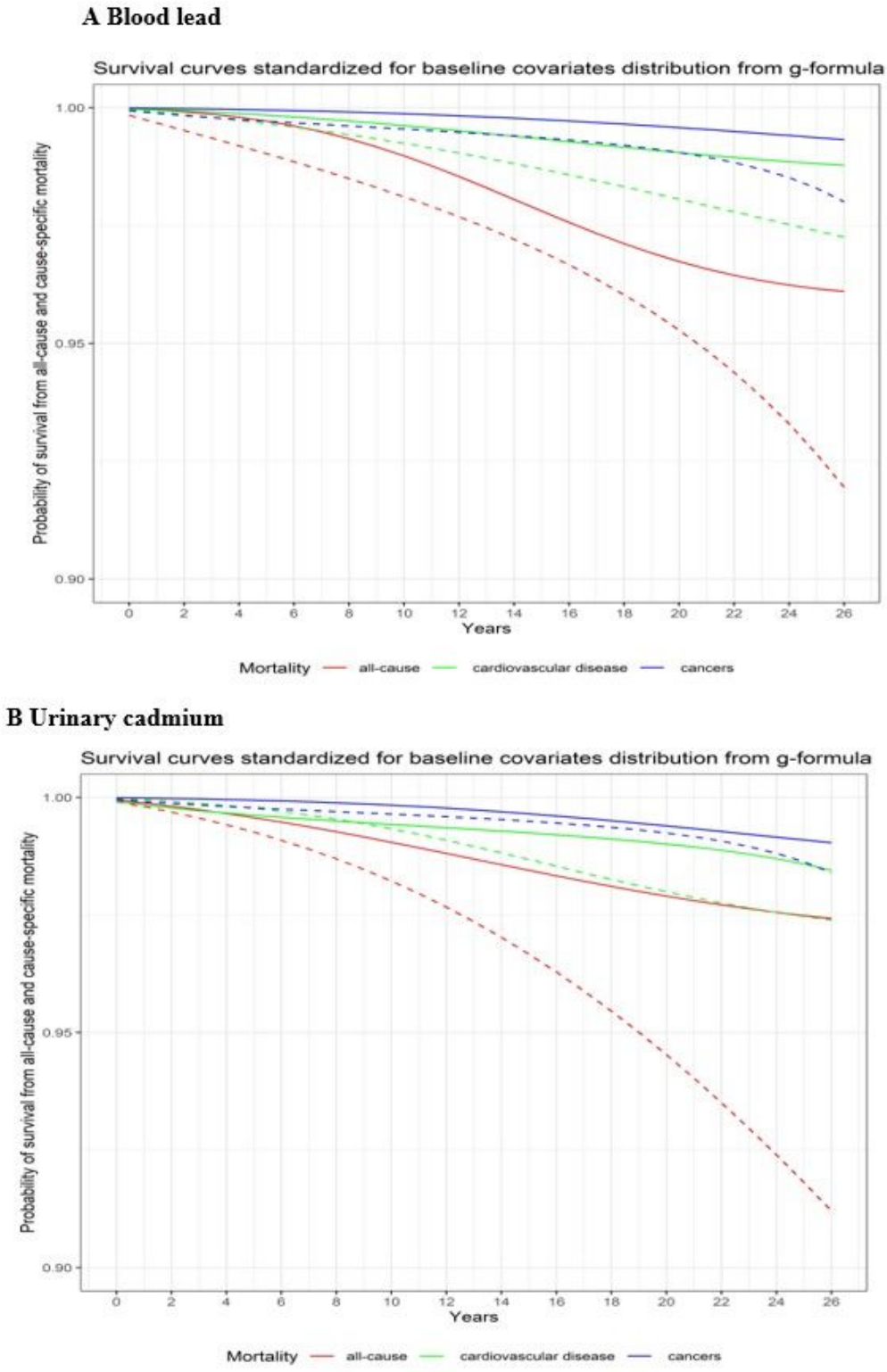

Figure 1

Adjusted all-cause, cardiovascular disease and cancer mortality risks according to blood lead (A) and urinary cadmium (B) levels using parametric g-formula with pooled logistic regression models. The solid line represents the percentile 5 (0.70 µg/dL for lead and 0.04 µg/L for cadmium) and the dashed lines the percentile 95 (9.70 µg/dL for lead and 1.63 µg/L for cadmium). Robust 95% confidence intervals (CIs) for

each exposure category estimated by bootstrapping (in the pooled logistic regression model) are presented in Table 2.

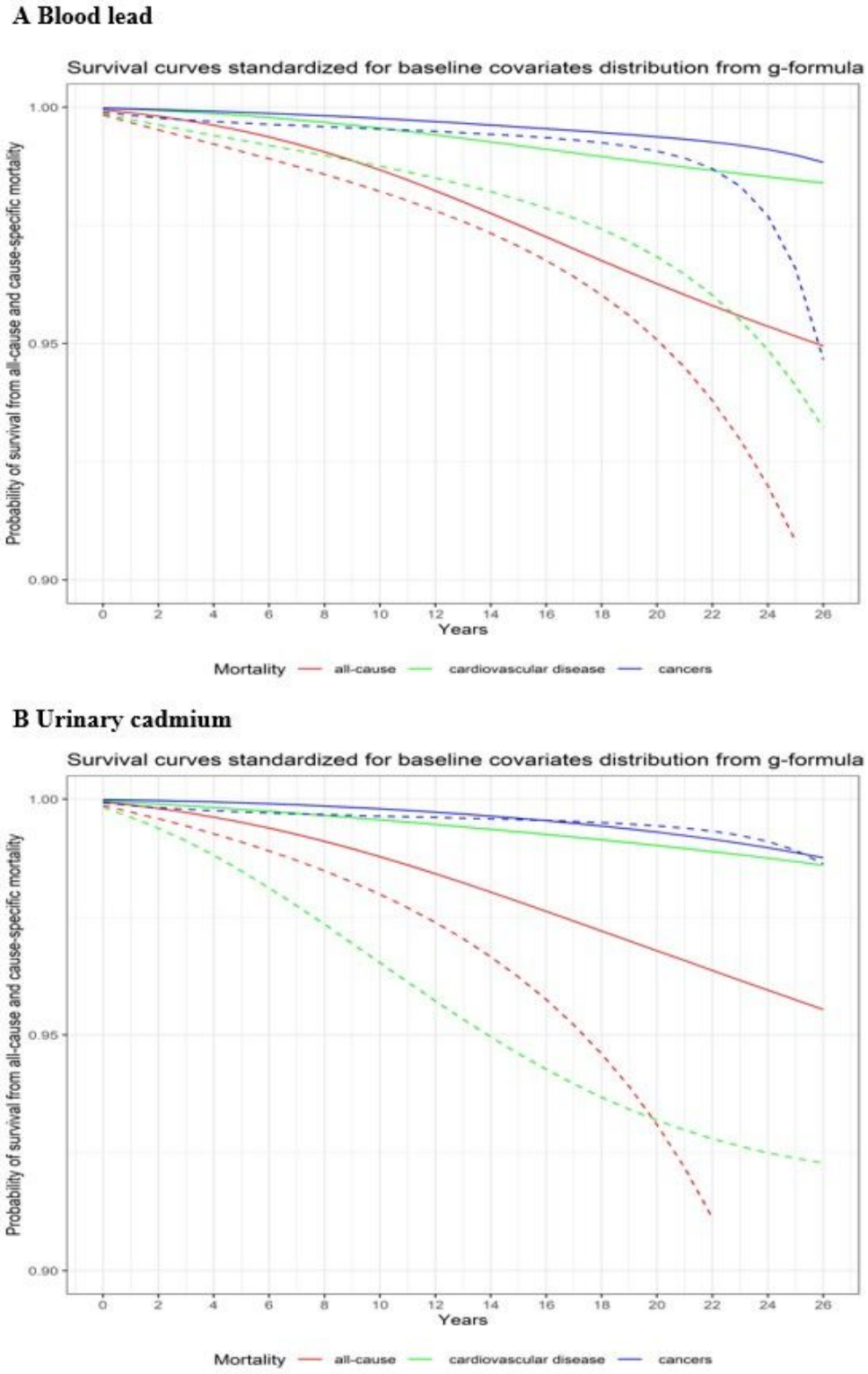

Figure 2

Adjusted all-cause, cardiovascular disease and cancer mortality risks according to blood lead (A) and urinary cadmium (B) levels using parametric g-formula with pooled logistic regression models. The solid

line represents the quartile 1 and the dashed lines the quartile 4. Robust 95% confidence intervals (CIs) for each exposure category estimated by bootstrapping (in the pooled logistic regression model) are presented in Table 3.

Supplementary Files

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- SupplementalMethods.docx