



Associations of exposure to lead and cadmium with risk of all-cause and cardiovascular disease mortality among patients with type 2 diabetes

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Abstract

The aim of this paper is to investigate the associations of lead and cadmium exposure with all-cause and cardiovascular disease (CVD) mortality among adults with type 2 diabetes (T2D). The prospective cohort study included participants with T2D ($n = 7420$ for blood lead; $n = 5113$ for blood cadmium) from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2014. Death outcomes were ascertained through linkage with the National Death Index records. The geometric mean (interquartile range) concentrations of blood lead and cadmium were 19.6 (11.8, 35.0) $\mu\text{g/L}$ and 0.39 (0.21, 0.60) $\mu\text{g/L}$, respectively. During 72,279 and 37,017 person-years of followup, 2818 all-cause deaths (including 832 CVD deaths) for blood lead and 1237 all-cause deaths (including 319 CVD deaths) for blood cadmium were documented, respectively. Comparing extreme quartiles, the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality were 1.51 (1.25, 1.82) for blood lead ($P_{\text{trend}} < 0.001$) and 1.58 (1.22, 2.03) for blood cadmium ($P_{\text{trend}} < 0.001$); and the HRs (95% CIs) of CVD mortality were 2.27 (1.54, 3.34) for blood lead ($P_{\text{trend}} < 0.001$) and 1.78 (1.04, 3.03) for blood cadmium ($P_{\text{trend}} = 0.07$). In the joint analysis, compared with participants in the lowest tertiles of blood lead and cadmium, participants in the highest tertiles had a HR (95% CI) of 2.09 (1.35, 3.24) for all-cause mortality. Exposure to lead and cadmium alone or in combination was significantly associated with higher risk of mortality among patients with T2D. These findings imply that minimizing exposure to lead and cadmium may aid in the prevention of premature death among individuals with diabetes.

Keywords Lead · Cadmium · Mortality · Prospective study · Type 2 diabetes

Abbreviations

BMI	Body mass index	ICP-MS	Inductively coupled plasma mass spectrometry
eGFR	Estimate glomerular filtration rate	NCHS	National Center for Health Statistics
ICP-DRC-MS	Inductively coupled plasma dynamic reaction cell mass spectrometry	NHANES	National Health and Nutrition Examination Survey
		T2D	Type 2 diabetes

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Introduction

T2D has been a global public health concern with an estimation of 463 million adults living with diabetes in 2019 (Saeedi et al. 2019). Patients with diabetes had a 2–4 times higher risk of developing cardiovascular disease (CVD) and mortality compared with people without diabetes (Cosentino et al. 2020; Harding et al. 2019; Standl et al. 2019). Emerging evidence has suggested that environmental contaminants could be involved in the development of diabetes complications and premature death (Calderon Moreno et al. 2019; Hagedoorn et al. 2020; Lanphear et al. 2018; Satarug et al. 2020; Tellez-Plaza et al. 2012).

Lead and cadmium are listed as two common heavy metal pollutants by World Health Organization (Satarug et al. 2020; WHO 2021). The main source of exposure to lead and cadmium is from ambient air, smoking (Chen et al. 2019), and contaminated diet (Satarug et al. 2020) in the general population. Although epidemiological studies indicated that chronic exposure to lead and cadmium was associated with increased risk of diabetes (Schwartz et al. 2003; Wan et al. 2021a), CVD (Navas-Acien et al. 2007, 2004; Tellez-Plaza et al. 2013), renal impairment (Muntner et al. 2003), and mortality (Lanphear et al. 2018; Satarug et al. 2020; Schober et al. 2006; Tellez-Plaza et al. 2012) in general populations, evidence is scarce regarding the impact of lead and cadmium exposure on the long-term health outcomes among patients with diabetes, who are particularly susceptible to renal dysfunction or metabolic disorders (Koye et al. 2018). Only two prospective studies among approximately 200 patients with diabetes and hemodialysis treatment suggested a positive association of exposure to lead and cadmium with all-cause mortality (Lin et al. 2008; Yen et al. 2011), with the limitations of small sample size, poor representativeness of study population, and insufficient adjustment of significant confounders (e.g., diabetes duration, diabetes medication use, and comorbidities). In addition, previous study has suggested that lead and cadmium usually coexist in the environment and may have synergic effect on nephrotoxicity (Satarug et al. 2020); however, no research has examined the joint association of lead and cadmium exposure with risk of mortality among patients with diabetes.

To fill the research gaps, we aimed to investigate the associations of exposure to lead and cadmium, individually and in combination, with all-cause and CVD mortality in adults with T2D.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES), which is conducted by the National Center for Health Statistics (NCHS), collected information about nationally representative samples of the non-institutionalized population-based participants in USA to evaluate national health and nutrition status (CDC 2022b). The protocol of NHANES was approved by the research ethics review board of the NCHS, and all participants provided oral and written informed consent.

The current study included participants with diabetes (age ≥ 20 years) from NHANES III (1988–1994) and eight cycles of NHANES from 1999 to 2014. Diabetes was defined as self-reported physician diagnosis of diabetes, use of insulin or oral hypoglycemic medication, fasting glucose ≥ 7.0 mmol/L, 2-h glucose ≥ 11.0 mmol/L, or glycated hemoglobinA_{1c} (HbA_{1c}) $\geq 6.5\%$ (48 mmol/mol), according to American Diabetes Association criteria in 2020 (ADA 2020).

The study included 8548 patients with diabetes for blood lead analysis and 5945 patients with diabetes for blood cadmium analysis (data on blood cadmium was not available in NHANES III). After excluding those who were pregnant ($n = 27$ for lead and $n = 20$ for cadmium), had cancer at baseline ($n = 1089$ for lead and $n = 807$ for cadmium), or lacked information on mortality ($n = 12$ for lead and $n = 5$ for cadmium), 7420 participants were included in blood lead analysis, and 5113 participants were included in blood cadmium analysis. Flowchart of the study population is shown in Supplementary Fig. 1.

Measurement of blood lead and cadmium

The measurements of blood lead and cadmium concentrations were performed in the Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention. Individuals with levels below the limit of detection were imputed as the limit of detection divided by the square root of 2. Detailed information on laboratory quality assurance and monitoring is available at <https://www.cdc.gov/nchs/nhanes/index.htm>.

Blood lead was measured by graphite furnace atomic absorption spectrophotometry in NHANES III (1988–1994), atomic absorption spectrometer with Zeeman background correction in NHANES 1999–2002, and inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) in NHANES 2003–2014.

The concentration of blood lead was expressed as micrograms per liter ($\mu\text{g/L}$). Besides, blood cadmium concentration was measured by atomic absorption spectrometer with Zeeman background correction in NHANES 1999–2002, and ICP-DRC-MS spectrometer in NHANES 2003–2014. The concentration of blood cadmium was expressed as micrograms per liter ($\mu\text{g/L}$). In addition, urinary cadmium was measured by graphite furnace atomic absorption spectrophotometry in NHANES III, ICP-MS in NHANES 1999–2002 and ICP-DRC-MS in NHANES 2003–2014. After correction for different dilutions of spot samples, urinary cadmium concentration was described as urinary cadmium/urine creatinine ($\mu\text{g/g}$) (Schwartz et al. 2003).

Ascertainment of mortality

Deaths were obtained through the linkage of the cohort with the National Death Index until 31st December 2015. All-cause mortality was defined as any reason of death while CVD mortality was defined as International Classification of Diseases tenth version (ICD-10) codes I00–I09, I11, I13, I20–I51, and I60–I69.

Assessment of covariates

Standardized questionnaires were used to collect information on demographics and lifestyle factors, including age, sex, race/ethnicity, education, family income, smoking status, drinking status, and physical activity. Alcohol intake, weight, and height were acquired during physical examination at mobile examination centers. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Family income–poverty ratio was calculated as the total family income divided by the poverty threshold, reflecting the annual family income relative to the federal poverty level, and the ratio was classified as 0–1.0, 1.0–3.0, or 3.0 (Oduyayo et al. 2017). Never smokers were defined as self-reported smoking less than 100 cigarettes in their lifetime. Participants who had smoked over 100 cigarettes during their lifetime and reported smoking at the time of the interview were considered as current smokers. Former smokers were defined as those who smoked over 100 cigarettes and had quit smoking. Drinking status was classified as nondrinker and drinker. Drinker was further categorized as low-to-moderate drinker (< 2 drink per day in men and < 1 per day in women) and heavy drinker (≥ 2 drink per day in men and ≥ 1 per day in women). Physical activity was classified as inactive (no reported leisure-time physical activity), insufficiently active (the frequency of self-reported leisure-time moderate activity is 3–5 times per week with metabolic equivalent ranging from 3 to 6 or 1 to 3 times per week with metabolic equivalent more than

6), and active (self-reported leisure-time moderate activity is more than the group of insufficiently active) (Beddhu et al. 2009). Dietary quality was assessed by healthy eating index score (HEI). HEI-1995 and HEI-2010 were applied for data in NHANES 1988–1994 and NHANES 1999–2014, respectively. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate estimated glomerular filtration rate (eGFR) (Levey et al. 2009).

Statistical analysis

Given the complexity of sampling design, our analysis took sample weights, clustering, and stratification into consideration in our analysis according to the NHANES statistical analysis guideline (CDC 2022a). Participant's person-years were calculated from the date of recruitment to the date of death or the end of follow-up (December 31st, 2015), whichever occurred first. Cox proportional hazards regression model was applied to examine the association of blood lead and cadmium with risk of all-cause and CVD mortality. Three multivariable models were constructed. Model 1 was adjusted for age (continuous), sex (male, or female), and race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other). Model 2 was further adjusted for BMI (< 25.0 , 25.0 – 29.9 , or ≥ 30.0 kg/m^2), education level (less than high school, high school or equivalent, or college or above), family income–poverty ratio (0–1.0, 1.0–3.0, or > 3.0), drinking status (nondrinker, low to moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), and healthy eating index (in tertiles). Model 3 was further adjusted for duration of diabetes (≤ 3 , 3–10, or > 10 years), diabetes medication use (none, only oral medication, insulin, or others), HbA_{1c} ($< 7\%$, or $\geq 7\%$ [< 53 mmol/mol , or ≥ 53 mmol/mol]), self-reported hypertension, hypercholesterolemia, and CVD (yes or no), and renal function (eGFR < 90 , or ≥ 90 $\text{mL/min per } 1.73$ m^2). In addition, lead and cadmium (Pearson's correlation coefficient was 0.20) were also mutually adjusted in model 3. Median value of each category was treated as a continuous variable to estimate the linear trend. In addition, the joint association of blood lead and cadmium with risk of all-cause and CVD mortality was also evaluated (because of limited cases of CVD mortality in each group, the result was not shown). Multiple imputation method was applied for missing values of the above covariates (Yuan 2011).

Restricted cubic spline regression with three knots (25th, 50th, 75th) was fitted to explore the dose–response relationship between blood lead and cadmium and mortality. Stratified analyses were conducted by age (≤ 60 or > 60 years), sex (female or male), race (white or non-white), smoking status (never smoker or ever smoker), BMI (< 30 or ≥ 30.0 kg/m^2),

physical activity (inactive or insufficiently active or active), duration of diabetes (≤ 3 or > 3 years), and renal function (eGFR < 90 , or ≥ 90 mL/min per 1.73 m²). *P* values for the cross-product terms of stratified factors and exposures were used to examine the significance of interactions.

To further test the robustness of the results, we conducted a series of sensitivity analyses. First, the consumption of fish and shell (in tertiles) were additionally adjusted to reduce potential influence of the food source of lead and cadmium (Falcó et al. 2006). Second, repeated analyses were performed when participants with CVD at baseline were excluded. Third, to minimize the potential reverse causation bias, we repeated the analyses excluding those died within 2 years of follow-up. Fourth, considering that different measurement methods of exposures, survey years, and occupation may influence the results of interest, we further adjusted for these variables in models. Furthermore, given that pro-inflammatory diet may influence the association of the interest, we further adjusted for dietary inflammatory index which was used to evaluate dietary inflammatory potential (Shivappa et al. 2014). Finally, although urinary cadmium, which could also reflect long-term health outcome, was only measured in one-third participants in NHANES 1999–2014 and all participants in NHANES III, we examined the association between urinary cadmium and mortality risk among participants with T2D ($n = 4056$).

Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC, USA) and R software, version 4.0.4 (R Foundation). Statistical significance was defined as two-sided *P* values < 0.05 .

Results

The study included 7420 participants (mean age, 57.8 years; 49.4% male) and 5113 participants (mean age, 57.9 years; 51.6% male) with diabetes for the analyses of blood lead and cadmium, respectively. The geometric mean was 19.58 (interquartile range [IQR], 11.81–35.02) $\mu\text{g/L}$ for blood lead and 0.39 (IQR, 0.21–0.60) $\mu\text{g/L}$ for blood cadmium. Participants with higher blood lead concentrations were more likely to be older, non-Hispanic black, smokers, and drinkers, and had higher prevalence of eGFR < 90 mL/min per 1.73 m², whereas those with higher blood cadmium status were more likely to be older, overweight, smokers, and drinkers (Table 1).

For blood lead analysis, 2818 deaths (including 832 CVD deaths) were documented during 72,279 person-years of follow-up. For blood cadmium analysis, 1237 deaths were recorded (including 319 CVD deaths) during 37,017 person-years of follow-up. After multivariable adjustment including demographic and lifestyle factors, diabetes duration, and HbA_{1c}, blood lead and cadmium concentrations were

positively associated with all-cause and CVD mortality in a dose-dependent manner. The multivariable-adjusted HRs (95% CIs) across quartiles of blood lead were 1.00 (reference), 1.20 (0.98, 1.46), 1.35 (1.10, 1.66), and 1.51 (1.25, 1.82) for all-cause mortality ($P_{\text{trend}} < 0.001$); and 1.00 (reference), 1.17 (0.78, 1.76), 1.44 (0.94, 2.22), and 2.27 (1.54, 3.34) for CVD mortality ($P_{\text{trend}} < 0.001$). The multivariable-adjusted HRs (95% CIs) across quartiles of blood cadmium were 1.00 (reference), 1.01 (0.75, 1.35), 1.24 (0.97, 1.60), and 1.58 (1.22, 2.03) for all-cause mortality ($P_{\text{trend}} < 0.001$); and 1.00 (reference), 1.42 (0.87, 2.32), 1.41 (0.87, 2.30), and 1.78 (1.04, 3.03) for CVD mortality ($P_{\text{trend}} = 0.07$). For per one-unit increment in natural log-transformed blood lead and cadmium, the multivariable-adjusted HRs (95% CIs) were 1.25 (1.16, 1.36) and 1.38 (1.21, 1.58) for all-cause mortality, and 1.55 (1.31, 1.82) and 1.29 (0.99, 1.64) for CVD mortality, respectively (Table 2).

A linear dose–response relationship was observed between blood lead (ranged from 1.85 to 126 $\mu\text{g/L}$) and all-cause and CVD mortality (both $P_{\text{linearity}} < 0.05$, Fig. 1A and Supplementary Fig. 2A). For blood cadmium, a non-linear association with all-cause mortality was demonstrated ($P_{\text{non-linearity}} = 0.004$), with a sharp increase in slope when blood cadmium concentration was more than about 0.60 $\mu\text{g/L}$ (Fig. 1B).

The joint associations of blood lead and cadmium with all-cause mortality are shown in Fig. 2. Compared with participants who were in the lowest tertiles of blood lead and cadmium, participants in the highest tertiles had a HR (95% CI) of 2.09 (1.35, 3.24) for all-cause mortality. No significant interaction between blood lead and cadmium with respect to all-cause mortality was identified ($P_{\text{interaction}} = 0.37$).

In sensitivity analyses, consistent results were observed after stratification by age, sex, race, smoking status, BMI, physical activity, diabetes duration, and renal function. No significant interaction was observed between blood lead and cadmium and the stratified factors on all-cause mortality (all $P_{\text{interaction}} > 0.05$) (Supplementary Tables 1–2). Similar results were observed when excluding participants who died within 2 years of follow-up (Supplementary Table 3). The results remained stable after excluding participants with CVD at baseline, although some of the associations did not reach statistical significance, probably due to reduced power (Supplementary Table 4). The result did not significantly change with further adjustment of the consumption of fish and shell (Supplementary Table 5), measurement methods of blood lead and cadmium (Supplementary Table 6), NHANES cycles (Supplementary Table 7), occupation (Supplementary Table 8), or dietary inflammatory index (Supplementary Table 9). In addition, urinary cadmium levels were positively associated with all-cause and cancer mortality. Compared with participants in the lowest quartiles, the HR (95% CIs) of participants in the highest tertiles was 1.58

Table 1 Baseline characteristics of participants with diabetes according to blood lead and cadmium concentrations in NHANES III and NHANES 1999–2014^{a, b}

	Blood lead concentrations (µg/L)			Blood cadmium concentrations (µg/L)		
	Total	Quartile 1 (< 11.81)	Quartile 4 (> 35.02)	Total	Quartile 1 (< 0.21)	Quartile 4 (> 0.60)
Number of patients	7420	1934	1694	5113	1056	1427
Age (mean ± SE), years	57.77 ± 0.27	53.00 ± 0.41	60.81 ± 0.45	57.91 ± 0.29	52.74 ± 0.55	58.88 ± 0.51
Female	3753 (50.6)	1227 (63.4)	645 (38.1)	2475 (48.4)	396 (37.5)	696 (48.8)
Race/ethnicity						
Non-Hispanic white	2592 (34.9)	668 (34.5)	519 (30.6)	1799 (35.2)	395 (37.4)	515 (36.1)
Non-Hispanic black	1997 (26.9)	438 (22.7)	575 (33.9)	1323 (25.9)	275 (26.0)	376 (26.4)
Mexican American	1921 (25.9)	495 (25.6)	488 (28.8)	1171 (22.9)	234 (22.2)	296 (20.7)
Others	910 (12.3)	333 (17.2)	112 (6.6)	820 (16.0)	152 (14.4)	240 (16.8)
BMI, kg/m²						
< 25.0	1200 (16.6)	209 (11.0)	380 (22.9)	705 (14.3)	108 (10.5)	293 (21.4)
25.0–29.9	2371 (32.7)	499 (26.4)	622 (37.5)	1527 (30.9)	277 (27.0)	461 (33.6)
≥ 30.0	3679 (50.7)	1185 (62.6)	655 (39.5)	2711 (54.9)	641 (62.5)	617 (45.0)
Drinking status						
Nondrinker	2317 (33.8)	759 (42.8)	347 (22.5)	1792 (38.0)	405 (41.0)	428 (32.9)
Low-to-moderate drinker	4170 (60.8)	974 (55.0)	1057 (68.5)	2661 (56.4)	541 (54.7)	763 (58.6)
Heavy drinker	375 (5.5)	41 (2.3)	139 (9.0)	264 (5.6)	43 (4.4)	112 (8.6)
Smoking status						
Never smoker	3579 (48.3)	1180 (61.1)	604 (35.7)	2530 (49.6)	778 (73.7)	331 (23.2)
Ever smoker	2501 (33.7)	533 (27.6)	658 (38.9)	1681 (32.9)	257 (24.4)	407 (28.6)
Current smoker	1332 (18.0)	220 (11.4)	431 (25.5)	894 (17.5)	20 (1.9)	687 (48.2)
Education levels						
Less than high school	3928 (54.0)	748 (39.0)	1238 (76.2)	2146 (42.1)	368 (34.9)	685 (48.2)
High school or equivalent	1344 (18.5)	424 (22.1)	177 (10.9)	1157 (22.7)	249 (23.6)	326 (22.9)
College or above	1997 (27.5)	748 (39.0)	210 (12.9)	1799 (35.3)	437 (41.5)	410 (28.9)
Family income-poverty ratio						
≤ 1.0	17 (26.1)	457 (26.0)	471 (31.2)	1155 (25.0)	218 (22.8)	411 (32.1)
1.0–3.0	3158 (47.4)	780 (44.3)	738 (48.9)	2154 (46.6)	442 (46.1)	604 (47.2)
> 3.0	1769 (26.5)	524 (29.8)	299 (19.8)	1315 (28.4)	298 (31.1)	266 (20.8)
Leisure-time physical activity						
Inactive	4016 (55.7)	1097 (57.9)	856 (52.2)	3059 (62.4)	564 (55.0)	936 (69.3)
Insufficiently active	2059 (28.6)	520 (27.4)	512 (31.2)	1145 (23.4)	299 (29.1)	250 (18.5)
Active	1133 (15.7)	278 (14.7)	273 (16.6)	698 (14.2)	163 (15.9)	165 (12.2)
Duration of diabetes						
≤ 3 years	3833 (53.3)	891 (47.6)	998 (60.5)	2435 (48.7)	494 (47.6)	697 (50.2)
3–10 years	1500 (20.9)	438 (23.4)	276 (16.7)	1152 (23.0)	261 (25.1)	310 (22.3)
> 10 years	1860 (25.9)	545 (29.1)	377 (22.8)	1414 (28.3)	283 (27.3)	382 (27.5)
HbA_{1c}						
< 7.0% (53 mmol/mol)	4203 (56.8)	971 (50.3)	1077 (63.8)	2816 (55.3)	552 (52.5)	828 (58.2)
≥ 7.0% (53 mmol/mol)	3193 (43.2)	961 (49.7)	612 (36.2)	2281 (44.8)	500 (47.5)	595 (41.8)
Self-reported diseases						
Hypertension	4324 (58.3)	1151 (59.5)	967 (57.1)	3179 (62.2)	613 (58.1)	878 (61.5)
Hypercholesterolemia	3181 (42.9)	988 (51.1)	514 (30.3)	2571 (50.3)	514 (48.7)	676 (47.4)
CVD	1568 (21.1)	346 (17.9)	398 (23.5)	1234 (24.1)	180 (17.1)	397 (27.8)
Renal function						
eGFR < 90 mL/min/1.73 m ²	4615 (63.9)	907 (48.2)	1330 (81.0)	2703 (54.2)	460 (44.7)	788 (56.8)

Table 1 (continued)

	Blood lead concentrations ($\mu\text{g/L}$)			Blood cadmium concentrations ($\mu\text{g/L}$)		
	Total	Quartile 1 (< 11.81)	Quartile 4 (> 35.02)	Total	Quartile 1 (< 0.21)	Quartile 4 (> 0.60)
eGFR \geq 90 mL/min/1.73 m ²	2609 (36.1)	976 (51.8)	312 (19.0)	2281 (45.8)	569 (55.3)	599 (43.2)
Healthy eating index						
Tertile1	2316 (33.2)	534 (29.3)	645 (40.8)	1560 (32.5)	335 (33.4)	550 (41.7)
Tertile2	2351 (33.7)	616 (33.8)	531 (33.6)	1603 (33.3)	320 (31.9)	416 (31.5)
Tertile3	2300 (33.0)	674 (37.0)	404 (25.6)	1645 (34.2)	347 (34.6)	353 (26.8)

^aBMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CVD, cardiovascular disease; eGFR, estimate glomerular filtration rate

^bContinuous variables were described as means \pm SE and categorical variables were characterized as numbers (percentages). All estimates accounted for complex survey design

Table 2 Hazard ratios (95% CIs) for all-cause and CVD mortality according to blood lead and cadmium concentrations among patients with diabetes in NHANES III and NHANES 1999–2014

	Quartiles				<i>P</i> trend	Per one-unit increment ^a
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Blood lead						
<i>All-cause mortality</i>						
Number of deaths/person years	304/149610	638/19010	765/18142	1111/20158		
Model 1	1	1.21 (0.97, 1.52)	1.38 (1.11, 1.73)	1.68 (1.37, 2.07)	<0.001	1.30 (1.18, 1.43)
Model 2	1	1.16 (0.95, 1.41)	1.26 (1.02, 1.55)	1.38 (1.13, 1.69)	0.004	1.17 (1.07, 1.28)
Model 3	1	1.20 (0.98, 1.46)	1.35 (1.10, 1.66)	1.51 (1.25, 1.82)	<0.001	1.25 (1.16, 1.36)
<i>CVD Mortality</i>						
Number of deaths	81	161	214	376		
Model 1	1	1.12 (0.76, 1.67)	1.39 (0.90, 2.14)	2.18 (1.49, 3.19)	<0.001	1.47 (1.27, 1.71)
Model 2	1	1.10 (0.74, 1.62)	1.33 (0.86, 2.06)	2.02 (1.37, 2.97)	<0.001	1.42 (1.20, 1.67)
Model 3	1	1.17 (0.78, 1.76)	1.44 (0.94, 2.22)	2.27 (1.54, 3.34)	<0.001	1.55 (1.31, 1.82)
Blood cadmium						
<i>All-cause mortality</i>						
Number of deaths/person years	160/8055	207/8156	380/10859	490/9948		
Model 1	1	1.03 (0.74, 1.42)	1.41 (1.06, 1.86)	2.01 (1.52, 2.65)	<0.001	1.55 (1.39, 1.74)
Model 2	1	1.04 (0.76, 1.42)	1.34 (1.02, 1.75)	1.65 (1.23, 2.22)	<0.001	1.42 (1.23, 1.64)
Model 3	1	1.01 (0.75, 1.35)	1.24 (0.97, 1.60)	1.58 (1.22, 2.03)	<0.001	1.38 (1.21, 1.58)
<i>CVD Mortality</i>						
Number of deaths	43	58	105	113		
Model 1	1	1.31 (0.78, 2.18)	1.43 (0.88, 2.31)	1.90 (1.15, 3.15)	0.01	1.37 (1.11, 1.70)
Model 2	1	1.40 (0.84, 2.34)	1.47 (0.91, 2.38)	1.76 (1.02, 3.04)	0.08	1.29 (1.01, 1.64)
Model 3	1	1.42 (0.87, 2.32)	1.41 (0.87, 2.30)	1.78 (1.04, 3.03)	0.07	1.29 (0.99, 1.66)

^aPer one-unit increment in natural log-transformed blood lead and cadmium

Model 1: adjusted for age (continuous), sex (male, or female), and race (non-Hispanic white, non-Hispanic black, Mexican American, or other)

Model 2: further adjusted (from model 1) for BMI (<25.0, 25.0–29.9, or \geq 30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (0–1.0, 1.0–3.0, or > 3.0), drinking status (nondrinker, low to moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group) and healthy eating index (in tertiles)

Model 3: further adjusted (from Model 2) for duration of diabetes (\leq 3, 3–10, or > 10 years), diabetes medication use (none, only oral medication, insulin, or others), HbA_{1c} (< 7%, or \geq 7% [$<$ 53 mmol/mol, or \geq 53 mmol/mol]), self-reported hypertension, hypercholesterolemia, and CVD (yes, or no), renal function (eGFR < 90, or \geq 90 mL/min/1.73 m²), and lead or cadmium (mutual adjustment in quartiles)

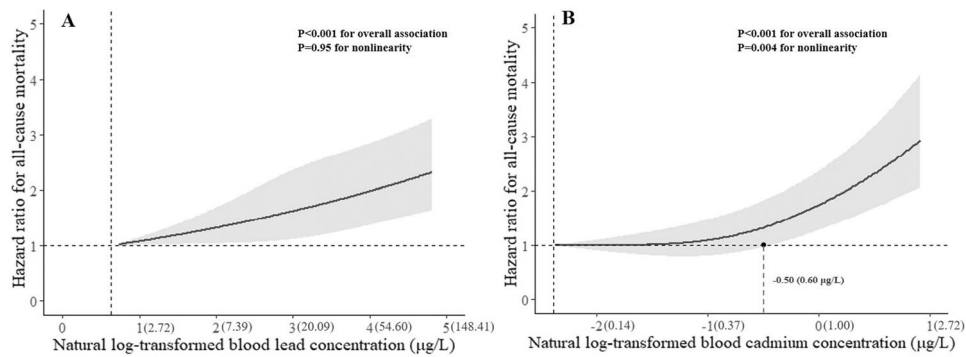


Fig. 1 Associations of blood lead (A) and cadmium (B) with all-cause mortality among patients with diabetes in NHANES III and NHANES 1999–2014. HRs were adjusted for age (continuous), sex (male, or female), race (non-Hispanic white, non-Hispanic black, Mexican American, or other), BMI (< 25.0, 25.0–29.9, or ≥ 30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (0–1.0, 1.0–3.0, or > 3.0), drinking status (nondrinker, low to moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or

current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), healthy eating index (in tertiles), duration of diabetes (≤ 3, 3–10, or > 10 years), diabetes medication use (none, only oral medication, insulin, or others), HbA_{1c} (< 7%, or ≥ 7% [< 53 mmol/mol, or ≥ 53 mmol/mol]), self-reported hypertension, hypercholesterolemia, and CVD (yes, or no), renal function (eGFR < 90, or ≥ 90 mL/min/1.73 m²), and lead or cadmium (mutual adjustment in quartiles)

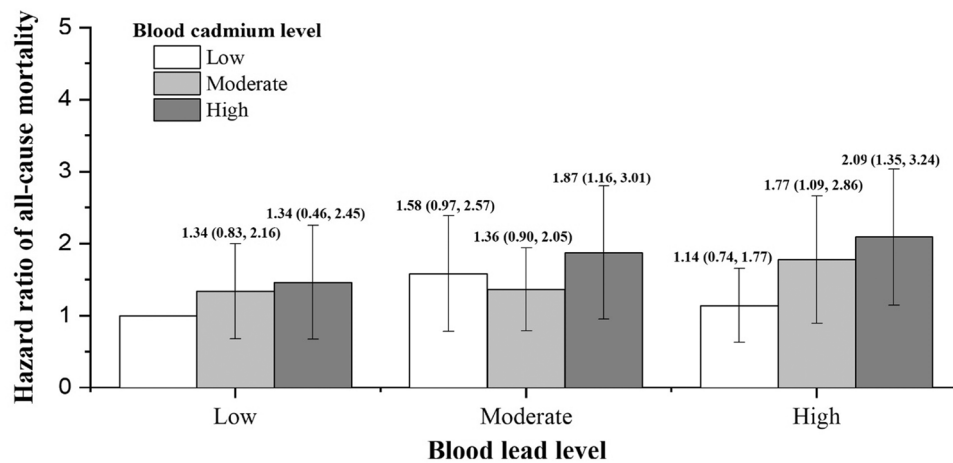


Fig. 2 The joint associations between blood lead level and/ or blood cadmium level and all-cause mortality among patients with diabetes ($n = 5113$). HRs were adjusted for age (continuous), sex (male, or female), race (non-Hispanic white, non-Hispanic black, Mexican American, or other), BMI (< 25.0, 25.0–29.9, or ≥ 30.0 kg/m²), education level (less than high school, high school or equivalent, or college or above), family income-poverty ratio (0–1.0, 1.0–3.0, or > 3.0), drinking status (nondrinker, low to moderate drinker, or heavy

drinker), smoking status (never smoker, former smoker, or current smoker), leisure-time moderate-to-vigorous physical activity (inactive group, insufficiently active group, or active group), healthy eating index (in tertiles), duration of diabetes (≤ 3, 3–10, or > 10 years), diabetes medication use (none, only oral medication, insulin, or others), HbA_{1c} (< 7%, or ≥ 7% [< 53 mmol/mol, or ≥ 53 mmol/mol]), self-reported hypertension, hypercholesterolemia, and CVD (yes, or no), and renal function (eGFR < 90, or ≥ 90 mL/min/1.73 m²)

(1.23, 2.04) for all-cause mortality and 1.99 (1.13, 3.44) for cancer mortality (Supplementary Tables 10 and 11).

Discussion

In this nationally representative sample of US adults with T2D, we found that exposure to blood lead and cadmium was both associated with higher risk of all-cause and CVD

mortality, independent of traditional risk factors including dietary and lifestyle factors, diabetes duration, and glucose control. In addition, our study suggested that joint exposure of blood lead and cadmium may aggravate the risk of premature death among individuals with diabetes.

As widespread environmental pollutants, lead and cadmium exposure were associated with higher risk of kidney disease (Edwards and Prozialeck, 2009), CVD (Navas-Acien et al. 2007; Tellez-Plaza et al. 2013), osteoporosis and bone

fractures (Engström et al. 2012), and mortality in general populations (Barregard et al. 2016; Lanphear et al. 2018; Tellez-Plaza et al. 2012). Although a greater reduction has been found in lead and cadmium exposures over the past decades, exposures to these toxic metals at low level are still prevalent (Menke et al. 2006; Shim et al. 2017). Several recent studies indicated that low levels of blood lead or cadmium were associated with a higher risk of mortality (Menke et al. 2006; Tellez-Plaza et al. 2012). For example, cadmium at relatively low levels of exposure, with geometric mean of blood at 0.44 µg/L, was associated with higher risk of all-cause and CVD mortality in a representative sample of US adults (Tellez-Plaza et al. 2012). Another study also showed that blood lead level lower than 5 µg/dL were associated with an increased risk of death from all-causes and CVD (Lanphear et al. 2018).

Among patients with diabetes, who have a higher prevalence of kidney dysfunction (Koye et al. 2018) and impaired metabolism of metal elements (Afridi et al. 2008), evidence regarding the long-term health impact of exposure to lead and cadmium is scarce. For example, among 212 patients with diabetes requiring maintenance hemodialysis Yen et al. found that higher blood cadmium level was associated with an elevated risk of all-cause mortality after 1.5 years of follow-up (Yen et al. 2011). In another study, among 211 patients with diabetes treated by long-term hemodialysis, patients with abnormal blood lead level (> 200 µg/L) had greater risk of 1-year mortality compared to those with low level (< 100 µg/L) (Lin et al. 2008). Of note, previous two studies among patients with diabetes requiring hemodialysis could not adequately represent people with diabetes, as those participants were in more severe stage of diabetes and the concentrations of blood lead and cadmium were relatively high because of disease status (mean level of blood lead: 137 µg/L; median level of blood cadmium: 0.87 µg/L). Moreover, previous studies did not take into consideration of some important confounders, such as diabetes duration, glucose control, and comorbidities. To the best of our knowledge, our study was the first one to investigate the prospective associations of exposure to lead and cadmium alone or in combination with risk of mortality in nationally representative samples of US adults with T2D. A linear dose–response relationship between blood lead and risk of all-cause and CVD mortality, and a non-linear positive association between blood cadmium and all-cause mortality were found. Furthermore, since people can be exposed to lead and cadmium simultaneously because of the coexistence of these two heavy metals in food and environment as mixtures (Wang and Fowler, 2008), the joint association of exposure to lead and cadmium was explored, and we found that patients with T2D in the highest tertiles of blood lead and cadmium had 2 times higher risk of mortality than those in the lowest tertiles. Consistent results were observed after

further stratification by other potential confounders, including age, sex, race, smoking status, renal function, physical activity, BMI, and diabetes duration. Besides, the association of urinary cadmium with CVD mortality among individuals with T2D did not reach statistical significance in our study, which was similar to some studies conducted in the general population (Duan et al. 2020; Kim et al. 2019). Meanwhile, previous studies suggested that compared to blood cadmium, urinary cadmium was more easily affected by kidney dysfunction (Gao et al. 2018). Hence, the relationship between urinary cadmium and CVD mortality might be confounded by renal dysfunction, although the results did not significantly change when further adjusted for eGFR. Nevertheless, more large prospective studies in different populations are needed to confirm these findings.

Although the exact mechanism underlying the association of exposure to lead and cadmium with mortality among patients with diabetes remains unclear, accumulating epidemiological and experimental studies indicated oxidative stress and chronic inflammation regarded as common toxic mechanism for lead and cadmium (Djokic et al. 2014; Matović et al. 2015; Tinkov et al. 2017). Moreover, lead and cadmium could exhibit pro-inflammatory characteristics and cause immune response dysfunctions (López-Vanegas et al. 2020; Tinkov et al. 2017). In addition, some evidences suggested that lead could induce increase in gluconeogenic gene expression, which was related to elevated fasting blood glucose (Leff et al. 2018; Whittle et al. 1983). In experimental studies, cadmium was illustrated to play a role in diabetes progression through damaging pancreatic β cells and reducing glucose tolerance (Schwartz et al. 2003). Nonetheless, more studies are warranted to elucidate the underlying mechanisms.

The strengths of current study include its prospective design, large sample size, and detailed information on potential confounders (such as demographic characteristics, socioeconomic status, diet, lifestyle factors, and comorbidities), as well as the national representativeness of US adults with diabetes, which facilitates the generalizability of our findings. Moreover, we not only examined individual metal exposure, but also analyzed the combined association of exposure to lead and cadmium on mortality among people with T2D. However, present study also has some limitations. First, blood lead and cadmium were measured only once. Studies with repeated measurements are needed to confirm our findings. Consistent results were observed for urinary cadmium as another long-term biomarker of cadmium exposure (Ruiz-Hernandez et al. 2017). Second, mortality outcomes obtained from the National Death Index with a probabilistic match might introduce the misclassification of fundamental cause of death while high accuracy of the method has been validated by previous studies (Menke et al. 2006; Wan et al. 2021b). Third, our study did not have detailed information

on severity of diabetes, although we have adjusted for diabetes medication use, duration of diabetes, and HbA_{1c} in the multivariable analyses. Fourth, evidence showed that DMT1 gene polymorphism was linked with inter-individual variations in blood lead and cadmium levels (Kayaaltı et al. 2015), and more studies are needed to examine whether the association of blood lead and cadmium with mortality can be modified by genetic background. Fifth, residual confounding cannot be entirely excluded, despite comprehensive adjustment for the potential confounders. Finally, causality cannot be determined because of the observational study design.

Conclusion

In a large prospective study of US adults with diabetes, we found that higher exposure level of blood lead and cadmium, alone and in combination, was significantly associated with elevated risk of all-cause and CVD mortality among patients with T2D. Our findings indicate that reducing exposure to lead and cadmium may lower the risk of premature death among patients with diabetes.

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Author contribution GL designed the research; KZ performed the analysis and wrote the manuscript; YZ wrote the manuscript; QL investigated the research; TG reviewed and edited the manuscript; RL reviewed the manuscript; ZW investigated the research; XZ conducted the analysis; YL conducted the analysis; LL validated the data; ZQ validated the data; MH reviewed and edited manuscript; LL reviewed manuscript; and AP reviewed and edited manuscript. All authors provided critical revisions of the draft and approved the submitted draft. The corresponding author affirms that all authors meet authorship criteria. GL has primary responsibility for final content.

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Availability of data and materials The National Health and Nutrition Examination Survey (NHANES) is an open-access resources, and data are available at <https://www.cdc.gov/nchs/nhanes>.

Declarations

Ethics approval and consent to participate The NHANES protocol was approved by the National Center for Health Statistics Institutional Review Board, and written informed consent was obtained.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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