Cardiovascular Diabetology

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Oxidative stress and inflammation mediate the adverse effects of cadmium exposure on all-cause and cause-specific mortality in patients with diabetes and prediabetes

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Abstract

Background The effect of cadmium exposure on mortality risk among individuals with diabetes and prediabetes remains unclear, particularly regarding potential mediation by oxidative stress and inflammation. This study aimed to investigate the associations of blood cadmium levels with all-cause, cardiovascular disease (CVD), and cancer mortality and the mediating effects of oxidative stress and inflammation biomarkers in patients with diabetes and prediabetes.

Methods In this prospective cohort study, we analyzed 17,687 adults with diabetes and prediabetes from the National Health and Nutrition Examination Survey (NHANES, 1999–2018). Nine biomarkers related to oxidative stress (gamma-glutamyl transferase [GGT], uric acid [UA], high-density lipoprotein [HDL], UA to HDL ratio [UHR]) and inflammation (neutrophil-lymphocyte ratio [NLR], monocyte-lymphocyte ratio [MLR], neutrophil-monocyte-lymphocyte ratio [NMLR], systemic inflammation response index [SIRI], systemic immune-inflammation index [SII]) were systematically assessed. Kaplan-Meier survival analysis, Cox proportional hazards models, and restricted cubic splines (RCS) were applied to evaluate the association of cadmium with mortality risk. Generalized linear models were used to assess the association of cadmium with oxidative stress and inflammation biomarkers, while Cox regression and RCS evaluated their effects on mortality. Causal mediation analysis identified biological pathways mediated by oxidative stress and inflammation. Stratified and sensitivity analyses were further employed to confirm the robustness of the results.

Results During 161,047.75 person-years of follow-up, 3562 deaths occurred, including 1214 from CVD and 680 from cancer. Higher blood cadmium levels were associated with increased risks of all-cause mortality (fully adjusted hazard ratio [HR]: 2.17; 95% confidence interval [CI] 1.69–2.79, comparing highest vs. lowest quartile), CVD mortality (HR 2.06; 95% CI 1.41–3.02), and cancer mortality (HR 2.38; 95% CI 1.47–3.85), without evidence of nonlinear relationship.

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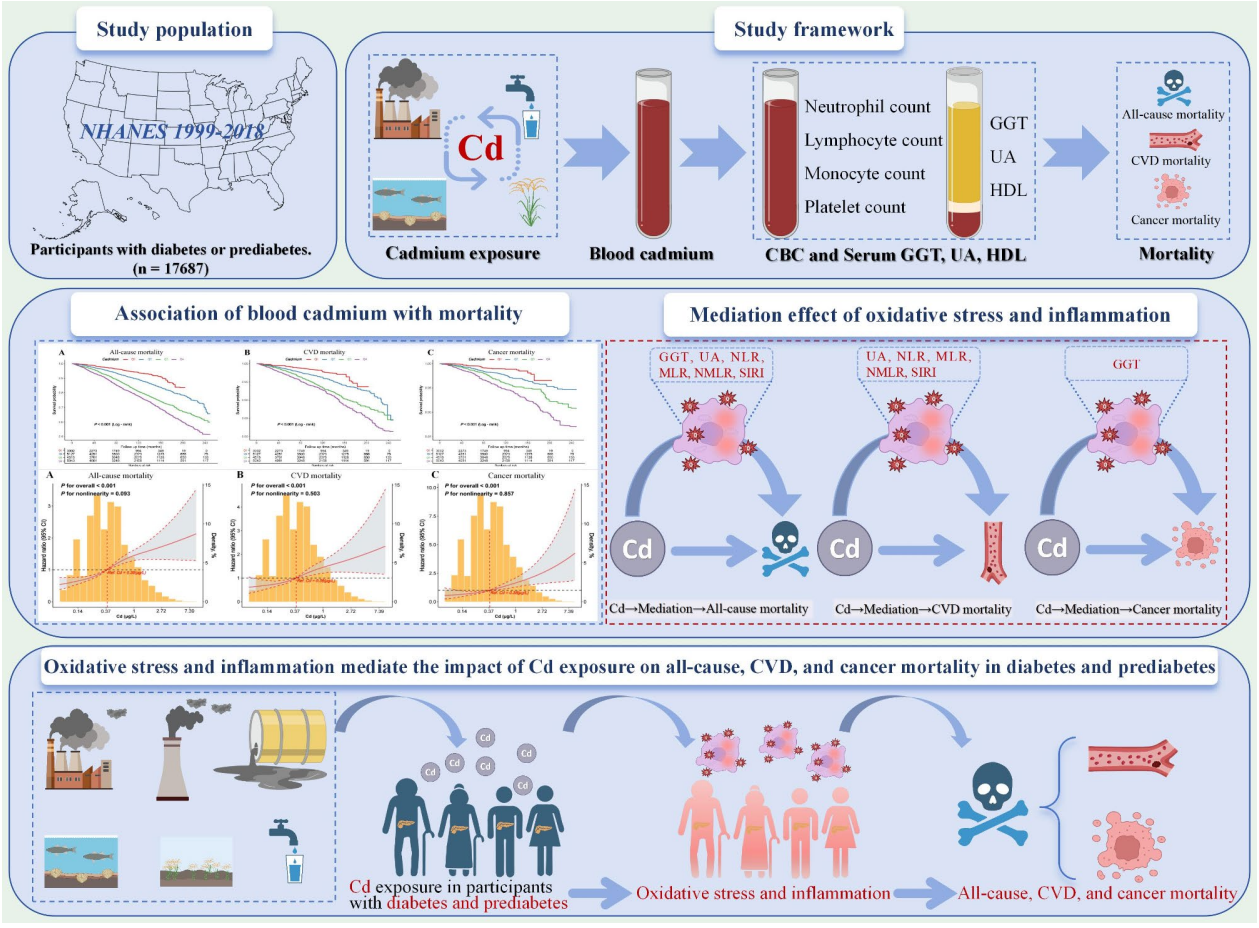
Mediation analyses indicated that UA, NLR, MLR, NMLR, and SIRI partially mediated the associations of cadmium with all-cause and CVD mortality, although the mediated proportions were relatively modest (ranging from 1.4 to 4.8%). Additionally, GGT mediated a small fraction of the associations with all-cause and cancer mortality.

Conclusion Cadmium exposure increases the risk of all-cause, CVD, and cancer mortality in patients with diabetes and prediabetes. Oxidative stress and inflammation appear to partially mediate this adverse effect. These findings emphasize the urgent need for targeted interventions to reduce cadmium-related mortality risks.

Graphical abstract



Research insights

What is currently known about this topic?

Cadmium exposure is linked to increased mortality. Oxidative stress and inflammation are critical in diabetes development and complications.

What is the key research question?

Does cadmium exposure increase mortality risk in patients with diabetes and prediabetes? Are oxidative stress and inflammation involved in mediating these effects?

What is new?

Cadmium exposure increases all-cause and cause-specific mortality in diabetes and prediabetes. Oxidative stress and inflammation mediate these associations.

How might this study influence clinical practice?

Monitor cadmium, oxidative stress, and inflammation to reduce mortality in diabetes and prediabetes.

Keywords Cadmium, Oxidative stress, Inflammation, Mortality, Diabetes, Prediabetes

Introduction

Diabetes has emerged as a significant global public health challenge, affecting approximately 537 million adults worldwide in 2021, with projections rising to 783 million by 2045 [1]. Prediabetes, an intermediate condition preceding diabetes, may impact up to 1 billion individuals globally by 2045, with around 10% annually progressing to diabetes in the United States [1, 2]. Individuals with diabetes and prediabetes are considered a vulnerable population, exhibiting significantly higher incidence and mortality rates from cardiovascular disease (CVD) and cancer compared to the general population [3–5]. Notably, although traditional risk factors such as hyperglycemia and dyslipidemia are well-characterized, emerging evidence highlights the role of environmental toxicants, particularly in metabolically vulnerable groups, where synergistic interactions with intrinsic oxidative stress and chronic inflammation may amplify mortality risk [6, 7]. Therefore, identifying modifiable environmental risk factors in diabetes and prediabetes is critical for targeted prevention.

Cadmium (Cd), a Group I carcinogen classified by the International Agency for Research on Cancer (IARC) [8], is a widespread environmental contaminant originating primarily from industrial activities, dietary intake, and tobacco use [9–11]. A recent scientific statement by the American Heart Association (AHA) emphasized that arsenic, lead, and Cd are established risk factors for coronary heart disease and stroke, though clinical recognition and interventions targeting metal exposure remain underdeveloped [12]. Cd is widely recognized for its cardiovascular and carcinogenic toxicities [13], with evidence from studies like the Multi-Ethnic Study of Atherosclerosis (MESA) and NHANES, which have linked Cd exposure to increased risks of all-cause, CVD, and cancer mortality in the general adult population of the United States [14–16]. However, the effect of Cd on mortality risk appears to be more complex in individuals with metabolic diseases, including diabetes. For instance, previous research found a significant positive association between Cd levels and CVD mortality among hypertensive individuals [17], whereas no significant associations were observed among patients with concurrent hypertension, diabetes, and coronary artery disease [18]. Additionally, it has been reported that in patients with type 2 diabetes, blood Cd levels as a continuous variable were not significantly associated with CVD mortality [19]. This inconsistency underscores a critical gap: the unique pathophysiology of diabetes, marked by oxidative stress, impaired antioxidant defenses like glutathione depletion, and chronic inflammation [20, 21], may heighten susceptibility to Cd-induced toxicity, potentially explaining differential mortality risks compared to the general population.

Oxidative stress and inflammation represent key mechanisms underlying Cd toxicity, processes that are also central in diabetes and prediabetes pathogenesis [21]. Cd disrupts cellular homeostasis by elevating reactive oxygen species (ROS) generation and promoting chronic inflammatory responses, thus exacerbating metabolic dysfunction and tissue injury [22–24]. In diabetic populations, Cd may further aggravate oxidative stress, potentially driving a vicious cycle that accelerates vascular endothelial injury and insulin resistance. Importantly, these pathological processes are quantifiable through blood biomarkers: Gamma-glutamyl transferase (GGT) and uric acid (UA) reflect glutathione metabolism and xanthine oxidase activity; high-density lipoprotein (HDL) cholesterol inversely correlates with lipid peroxidation [25–28]. Similarly, inflammation-related indices derived from complete blood counts, such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-monocyte-to-lymphocyte ratio (NMLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI), capture immune dysregulation characteristic of diabetes progression and Cd toxicity. These composite indices have been widely utilized to evaluate mortality risks and prognosis in metabolic disorders, CVD, and cancer [29–31].

Despite these established associations, several gaps remain in the current literature. First, most existing studies focus on the general adult population, with relatively little attention to individuals with diabetes or prediabetes. Second, epidemiological investigations clarifying the biological mechanisms linking Cd exposure to mortality risks remain scarce. Third, previous research typically relied on single inflammatory biomarkers (e.g., C-reactive protein) [32], neglecting composite indices that could better capture systemic oxidative stress and inflammatory status in diabetic populations. Fourth, no prior study has systematically assessed whether oxidative stress and inflammation mediate the association between Cd exposure and mortality. Mediation analysis offers a robust method to decompose the total effect into direct and indirect pathways, while accounting for potential interactions between exposure and mediators, thereby accommodating more complex analysis scenarios [33, 34]. Therefore, it is necessary to use this method to study the complex pathways between cadmium exposure and mortality risk.

Based on the above considerations, we hypothesize that Cd exposure is a significant risk factor for all-cause, CVD, and cancer mortality in individuals with diabetes and prediabetes, with oxidative stress and inflammation serving as potential mediators in this association. In this study, we utilized data from the National Health and Nutrition Examination Survey (NHANES, 1999–2018) linked to mortality records from the National Death

Index (NDI) through 2019. Using this nationally representative prospective cohort, we examined the associations of blood Cd levels with all-cause, CVD, and cancer mortality in individuals with diabetes and prediabetes. Additionally, we assessed the potential mediating effects of oxidative stress and inflammation biomarkers, including GGT, UA, HDL, UHR, NLR, MLR, NMLR, SIRI, and SII. The findings of this study will provide critical environmental epidemiological evidence to inform early prevention and intervention strategies for individuals with diabetes and prediabetes.

Methods

Study design

NHANES is a comprehensive program designed to assess the health and nutritional status of adults and children in the United States [35]. The study protocol was approved by the Ethics Review Committee of the National Center for Health Statistics (NCHS), and written informed consent was obtained from all adult participants. This study adhered strictly to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies to ensure rigor and transparency in reporting.

Study population

NHANES surveys approximately 5,000 participants annually. This study used data from 10 NHANES cycles (1999–2018), starting with 101,316 participants. After excluding individuals under 20 years old ($n = 46{,}235$), pregnant at the interview ($n = 1{,}216$), with a cancer diagnosis ($n = 5{,}144$), without diabetes or prediabetes ($n = 27{,}680$), missing blood Cd data ($n = 2{,}910$), follow-up information ($n = 39$), or oxidative stress and inflammation biomarker data ($n = 405$), the final cohort included 17,687 participants (Fig. S1).

Definition of diabetes and prediabetes

Diabetes was defined as meeting any of the following criteria: (1) self-reported physician-diagnosed diabetes ("Doctor told you have diabetes"); (2) current use of insulin; (3) current use of antidiabetic medications; (4) fasting plasma glucose (FPG) ≥ 126 mg/dL; or (5) glycated hemoglobin (HbA1c) ≥ 6.5%. Prediabetes was defined as meeting either of the following criteria [36]: (1) FPG between 100 and 125 mg/dL; or (2) HbA1c between 5.7 and 6.4%.

Blood cd levels

Blood Cd levels were measured using atomic absorption spectrometry (AAS) from 1999 to 2002 and inductively coupled plasma mass spectrometry (ICP-MS) from 2003 onward. All measurements adhered to laboratory quality control protocols. For values below the limit of detection (LLOD), Cd levels were recorded as LLOD / sqrt(2) to appropriately handle undetectable levels and minimize bias.

Oxidative stress and inflammation biomarkers

Oxidative stress biomarkers included GGT, UA, HDL, and UHR. Inflammatory biomarkers included NLR, MLR, NMLR, SII, and SIRI. Detailed calculation methods are provided in Table S1. GGT, UA, and HDL levels were measured using enzymatic kinetic methods, while complete blood counts (CBC) were obtained using Beckman Coulter technology, which classifies white blood cells based on volume, conductivity, and light scatter signals.

NHANES 1999–2018 linked mortality (1999–2019)

NHANES participant data were linked to the NDI using unique identifiers, and mortality outcomes were tracked through December 31, 2019. Cause of death was determined using ICD-10 codes, including all-cause mortality, CVD mortality (I00–I09, I11, I13, I20–I51, or I60–I69), and cancer mortality (C00–C97). Follow-up time was calculated from the survey date to either the date of death or the end of follow-up, whichever occurred first.

Covariates

Potential confounders were selected based on previous studies [15, 37, 38] and directed acyclic graph (DAG) analysis (Fig. S2). Trained interviewers administered standardized questionnaires to collect: (1) Demographic and socioeconomic information: age (≥ 20 & <60, ≥ 60), sex, race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other), education level (less than high school, high school/equivalent, college or above), marital status (married/living with partner, never married, widowed/divorced/separated), and family poverty-income ratio (PIR < 1.3, 1.3–3.5, ≥ 3.5). (2) Health behavior information: smoking status (never, former, current), alcohol consumption, and physical activity. Smoking status was defined as having smoked at least 100 cigarettes in a lifetime. Alcohol consumption was categorized according to the U.S. Dietary Guidelines (2020–2025) [39] as non-drinkers (0 g/day), moderate drinkers (0 < men ≤ 28 g/day, 0 < women ≤ 14 g/day), and excessive drinkers (men > 28 g/day, women > 14 g/day). Physical activity was classified into no activity, moderate activity, vigorous activity, and combined moderate/vigorous activity. Certified health technicians measured height, weight, and waist circumference following standardized protocols, and calculated body mass index (BMI) [weight (kg)/height (m^2)] and weight-adjusted waist index (WWI) [waist circumference (cm)/√weight (kg)]. Hypertension was defined as self-reported hypertension, average systolic blood pressure (SBP) ≥ 140 mmHg, and/or diastolic blood pressure (DBP) ≥ 90

mmHg. Kidney failure was determined by self-reported kidney dysfunction.

Statistical analysis

To account for the complex NHANES survey design, appropriate weights, stratification, and primary sampling units were applied to ensure nationally representative estimates. Continuous variables with non-normal distributions were presented as medians (interquartile range, IQR) and compared using the Kruskal-Wallis test. Categorical variables were reported as unweighted counts and weighted percentages, analyzed via Rao & Scott-adjusted Pearson chi-square tests. Missing data were handled using multiple imputations with 50 iterations. Kaplan-Meier (K–M) survival curves with log-rank tests compared cumulative mortality across Cd quartiles. Multivariable Cox proportional hazards regression models evaluated the associations of Cd exposure with all-cause, CVD, and cancer mortality. Given the right-skewed distribution, Cd concentrations were natural log-transformed and analyzed as both continuous and categorical variables. Participants were divided into quartiles according to the weighted distribution of blood Cd levels, using the lowest quartile (Q1) as the reference group. Trend tests were conducted using the median value of each quartile. Two stepwise adjusted models, aligned with STROBE guidelines, were developed: a partially adjusted model controlling for age, sex, and race; and a fully adjusted model further accounting for education level, marital status, PIR, BMI, WWI, smoking status, alcohol status, physical activity, failing kidneys, and hypertension. Proportional hazards assumptions were validated through Schoenfeld residuals, and model fit was assessed using the C-statistic. Multicollinearity was checked using variance inflation factors (VIFs).

To evaluate the exposure-response relationships between blood Cd levels and mortality risks, restricted cubic spline (RCS) models with four knots at the 5th, 35th, 65th, and 95th percentiles were applied. Consistent with mediation criteria [40], Cox regression was performed to examine the associations of oxidative stress and inflammation biomarkers (log-transformed and standardized) with all-cause, CVD, and cancer mortality. Generalized linear models (GLM) assessed the associations of blood Cd levels with oxidative stress and inflammation biomarkers. Prior to causal mediation analysis, several key assumptions were established to ensure reliability: a causal relationship between exposure (blood Cd levels), mediators (oxidative stress and inflammation biomarkers), and outcomes (mortality risks); linear relationships among these variables; and absence of unmeasured confounding factors influencing both mediator and outcome simultaneously. Based on these assumptions, causal mediation analysis with 1,000 bootstrap resamples was performed to estimate indirect effects and 95% confidence intervals, while interaction terms explored effect modification. Stratified analyses according to diabetes status and sex were also performed, examining individual effects and mediation pathways separately.

Several sensitivity analyses were conducted to ensure the robustness of the findings: (1) Fine-Gray subdistribution hazard models were used to address competing risks; (2) raw values from complete blood counts (CBC) were incorporated; (3) participants who died within two years of follow-up were excluded; (4) participants with follow-up durations exceeding 15 years were excluded; (5) missing values were re-imputed using a random forest algorithm; and (6) blood lead concentrations and occupational factors were individually included as additional covariates in the fully adjusted model. Moreover, considering existing evidence indicating kidney function and blood pressure as potential mediators between heavy metal exposure and mortality [41, 42], further sensitivity analyses were performed by excluding the variables of kidney failure and hypertension from the models to assess their impact on the primary results.

All analyses were performed using R software (version 4.4.1). A two-sided P-value < 0.05 was considered statistically significant.

Results

Descriptive statistics of baseline characteristics

A total of 17,687 participants with diabetes or prediabetes were included in this study. Table 1 presents the baseline characteristics for the overall population and across quartiles of weighted blood Cd levels. In the overall cohort, the majority were aged 20–60 years, male, non-Hispanic White, had a high school education, PIR ≥ 3.5, BMI ≥ 30 kg/m², were married or living with a partner, physically inactive, non-smokers, non-drinkers, without kidney failure but with hypertension. Compared to the lower Cd level group, participants in the higher Cd level group were more likely to be older (≥ 60 years), female, non-Hispanic Black or other races, with lower educational attainment, poorer economic status, BMI < 25 kg/m², higher WWI, widowed/divorced/separated, physically inactive, current smokers, excessive drinkers, and with kidney failure and hypertension. Additionally, we assessed the proportion of missing covariate data (Fig. S3) and performed descriptive analyses after multiple chained imputations (Tables S2 and S3).

[a] Median (Q1, Q3); n (%), unweighted numbers and weighted percentages shown.

[b] Design-based Kruskal-Wallis test; Pearson's c^2: Rao & Scott adjustment.

Table 1 Baseline characteristics of the selected participants in NHANES, 1999–2018

Variable	Overall (*n* = 17,687)	Quantile 1 (*n* = 3,002)[a]	Quantile 2 (*n* = 5,127)[a]	Quantile 3 (*n* = 4,515)[a]	Quantile 4 (*n* = 5,043)[a]	*P* value[b]
Age (years)						< 0.001
≥ 20 & <60	9,581 (63.12)	2,120 (78.47)	2,883 (63.86)	1,994 (51.15)	2,584 (61.52)	
≥ 60	8,106 (36.88)	882 (21.53)	2,244 (36.14)	2,521 (48.85)	2,459 (38.48)	
Sex, n (%)						< 0.001
Male	9,474 (53.29)	1,982 (67.26)	2,830 (55.09)	2,014 (42.49)	2,648 (50.50)	
Female	8,213 (46.71)	1,020 (32.74)	2,297 (44.91)	2,501 (57.51)	2,395 (49.50)	
Race, n (%)						< 0.001
Mexican American	3,498 (8.76)	656 (11.61)	1,159 (9.84)	944 (8.74)	739 (5.52)	
Other Hispanic	1,622 (5.98)	391 (7.10)	488 (6.34)	433 (6.44)	310 (4.39)	
Non-Hispanic White	6,630 (63.42)	1,081 (63.65)	1,824 (63.99)	1,629 (61.68)	2,096 (64.12)	
Non-Hispanic Black	4,213 (13.39)	664 (11.57)	1,255 (13.28)	1,042 (13.56)	1,252 (14.68)	
Other Race	1,724 (8.45)	210 (6.07)	401 (6.55)	467 (9.59)	646 (11.29)	
Education level, n (%)						< 0.001
Less than high school	5,900 (22.45)	808 (15.78)	1,575 (18.71)	1,573 (24.15)	1,944 (29.93)	
High school or equivalent	8,709 (55.21)	1,546 (56.40)	2,469 (53.53)	2,172 (54.21)	2,522 (57.06)	
College or above	3,044 (22.34)	644 (27.82)	1,075 (27.76)	763 (21.64)	562 (13.01)	
Missing	34 (0.14)	4 (0.07)	8 (0.08)	7 (0.08)	15 (0.30)	
PIR, n (%)						< 0.001
< 1.3	5,253 (23.22)	769 (18.52)	1,322 (18.53)	1,273 (22.60)	1,889 (32.37)	
≥ 1.3 & <3.5	6,284 (37.63)	1,093 (36.27)	1,796 (35.20)	1,646 (39.11)	1,749 (40.03)	
≥ 3.5	4,466 (39.15)	849 (45.20)	1,548 (46.27)	1,154 (38.29)	915 (27.59)	
Missing	1,684 (7.71)	291 (6.77)	461 (7.73)	442 (7.94)	490 (8.15)	
BMI (kg/m^2)						< 0.001
< 25	3,355 (18.65)	375 (13.01)	760 (14.53)	842 (18.85)	1,378 (27.14)	
≥ 25 & <30	5,864 (33.46)	919 (31.53)	1,714 (33.66)	1,537 (34.57)	1,694 (33.70)	
≥ 30	8,119 (47.89)	1,670 (55.45)	2,564 (51.81)	2,028 (46.59)	1,857 (39.16)	
Missing	349 (1.66)	38 (0.94)	89 (1.60)	108 (1.90)	114 (2.04)	
WWI (cm/kg$^{1/2}$)	11.22 (10.71, 11.76)	11.13 (10.58, 11.65)	11.22 (10.72, 11.74)	11.28 (10.80, 11.80)	11.27 (10.72, 11.82)	< 0.001
Marital status, n (%)						< 0.001
Married / Living with partner	10,732 (64.69)	1,955 (67.57)	3,275 (67.56)	2,748 (65.57)	2,754 (58.69)	
Widowed / Divorced / Separated	4,677 (23.02)	539 (15.14)	1,184 (20.16)	1,315 (25.96)	1,639 (29.37)	
Never married	2,151 (12.28)	507 (17.28)	618 (12.28)	415 (8.47)	611 (11.94)	
Missing	127 (0.79)	1 (0.02)	50 (1.01)	37 (0.81)	39 (1.08)	
Physical activity, n (%)						< 0.001
Inactive	7,099 (42.73)	1,356 (42.21)	1,921 (39.49)	1,709 (40.22)	2,113 (49.31)	
Moderate	4,706 (34.37)	769 (29.89)	1,407 (34.62)	1,256 (38.23)	1,274 (34.48)	
Vigorous	1,114 (7.66)	212 (7.99)	401 (9.11)	276 (7.56)	225 (5.71)	
Both moderate and vigorous	1,898 (15.24)	489 (19.91)	621 (16.78)	431 (13.99)	357 (10.50)	
Missing	2,870 (14.35)	176 (4.69)	777 (13.24)	843 (16.94)	1,074 (20.28)	
Smoking status, n (%)						< 0.001
Never	9,125 (50.53)	2,269 (74.40)	3,401 (65.04)	2,363 (50.13)	1,092 (17.69)	
Former	4,965 (28.54)	671 (23.79)	1,504 (31.28)	1,626 (37.55)	1,164 (21.24)	
Now	3,576 (20.93)	61 (1.80)	218 (3.69)	519 (12.32)	2,778 (61.07)	
Missing	21 (0.09)	1 (0.02)	4 (0.07)	7 (0.09)	9 (0.18)	
Alcohol status, n (%)						0.011
None	13,210 (77.36)	2,256 (76.26)	3,915 (78.41)	3,443 (78.63)	3,596 (75.87)	
Moderate	1,414 (8.89)	242 (9.39)	426 (8.98)	353 (9.20)	393 (8.14)	
Excessive	1,981 (13.75)	336 (14.35)	533 (12.61)	449 (12.18)	663 (15.99)	
Missing	1,082 (6.23)	168 (5.60)	253 (5.13)	270 (5.69)	391 (8.34)	
Failing kidneys, n (%)						< 0.001
Yes	713 (3.19)	75 (1.73)	175 (2.72)	206 (3.85)	257 (4.20)	
No	16,934 (96.81)	2,922 (98.27)	4,941 (97.28)	4,296 (96.15)	4,775 (95.80)	

Table 1 (continued)

Variable	Overall ($n=17,687$)	Quantile 1 ($n=3,002$)[a]	Quantile 2 ($n=5,127$)[a]	Quantile 3 ($n=4,515$)[a]	Quantile 4 ($n=5,043$)[a]	*P* value[b]
Missing	40 (0.16)	5 (0.14)	11 (0.16)	13 (0.19)	11 (0.17)	
Hypertension, n (%)						< 0.001
Yes	9,852 (53.44)	1,448 (46.79)	2,792 (53.18)	2,700 (57.76)	2,912 (54.82)	
No	7,379 (46.56)	1,482 (53.21)	2,198 (46.82)	1,702 (42.24)	1,997 (45.18)	
Missing	456 (2.63)	72 (2.29)	137 (2.44)	113 (2.38)	134 (3.30)	

PIR, Poverty impact ratio; BMI, Body mass index; WWI, Weight-adjusted waist index

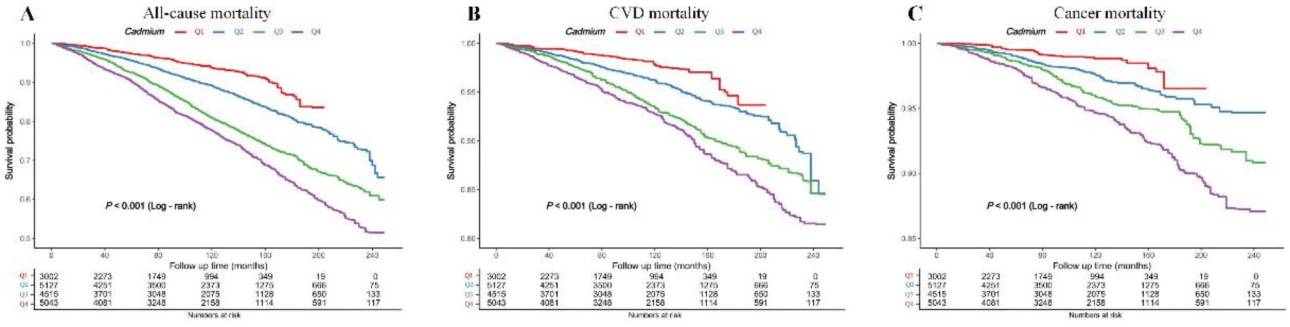


Fig. 1 K–M curves for **A** all-cause, **B** CVD, and **C** cancer mortality across quartiles of blood Cd

Table 2 Associations of blood cd levels with all-cause, CVD, and cancer mortality

	Blood Cadmium Levels[a], HR (95% CI)				*P* for trend[b]	Per ln-unit increase[c]
	Quantile 1	Quantile 2	Quantile 3	Quantile 4		
All-cause mortality, No.	202 / 3,002	781 / 5,127	1,099 / 4,515	1,480 / 5,043		
Partially adjusted[d]	1.00 (Ref.)	1.38 (1.09, 1.74)	1.85 (1.49, 2.30)	2.79 (2.22, 3.49)	< 0.001	1.57 (1.49, 1.67)
Fully adjusted[e]	1.00 (Ref.)	1.36 (1.10, 1.69)	1.75 (1.42, 2.15)	2.17 (1.69, 2.79)	< 0.001	1.45 (1.32, 1.59)
CVD mortality, No.	71 / 3,002	270 / 5,127	384 / 4,515	489 / 5,043		
Partially adjusted	1.00 (Ref.)	1.27 (0.91, 1.78)	1.55 (1.10, 2.17)	2.31 (1.67, 3.19)	< 0.001	1.46 (1.33, 1.60)
Fully adjusted	1.00 (Ref.)	1.31 (0.93, 1.85)	1.57 (1.11, 2.21)	2.06 (1.41, 3.02)	< 0.001	1.43 (1.25, 1.64)
Cancer mortality, No.	35 / 3,002	144 / 5,127	197 / 4,515	304 / 5,043		
Partially adjusted	1.00 (Ref.)	1.57 (0.99, 2.49)	2.18 (1.40, 3.39)	3.59 (2.31, 5.59)	< 0.001	1.79 (1.60, 2.00)
Fully adjusted	1.00 (Ref.)	1.45 (0.91, 2.31)	1.82 (1.17, 2.81)	2.38 (1.47, 3.85)	< 0.001	1.60 (1.36, 1.88)

CVD mortality, Cardiovascular disease mortality; HR, Hazard ratio

Association of blood cd levels with all-cause, CVD, and cancer mortality

Over 161,047.75 person-years of follow-up, 3,562 deaths were recorded, including 1,214 from CVD and 680 from cancer. Kaplan–Meier survival curves (Fig. 1) illustrate differences in cumulative mortality across quartiles of weighted blood Cd concentrations, with those in the highest quartile (Q4) experiencing higher mortality rates compared with the lowest quartile (Q1) (log-rank test, $P < 0.001$).

Table 2 presents the associations of Cd (log-transformed and quartile-based) with all-cause, CVD, and cancer mortality from Cox regression models. In the partially adjusted model, the highest Cd quartile was associated with significantly elevated risks of all-cause mortality (HR: 2.79, 95% CI: 2.22–3.49), CVD mortality (HR: 2.31, 95% CI: 1.67–3.19), and cancer mortality (HR: 3.59, 95% CI: 2.31–5.59) (*P* for trend < 0.001).

In the fully adjusted model, the highest Cd quartile remained significantly associated with increased risks of all-cause mortality (HR: 2.17, 95% CI: 1.69–2.79), CVD mortality (HR: 2.06, 95% CI: 1.41–3.02), and cancer mortality (HR: 2.38, 95% CI: 1.47–3.85). Per unit increase in log-transformed Cd levels was associated with a 45% (95% CI: 32–59%) increase in all-cause mortality, a 43% (95% CI: 25–64%) increase in CVD mortality, and a 60% (95% CI: 36–88%) increase in cancer mortality. The PH assumption was validated using the Schoenfeld residual test ($P = 0.221$, 0.273, and 0.777 for all-cause, CVD, and cancer mortality, respectively). Model performance was robust, with C-statistics exceeding 0.7 across all models, indicating a good fit. Variance inflation factors (VIFs) were below 5, suggesting no significant multicollinearity (Table S4).

[a] Cut-off values for blood Cd quantiles were determined by the weighted distributions in the study sample.

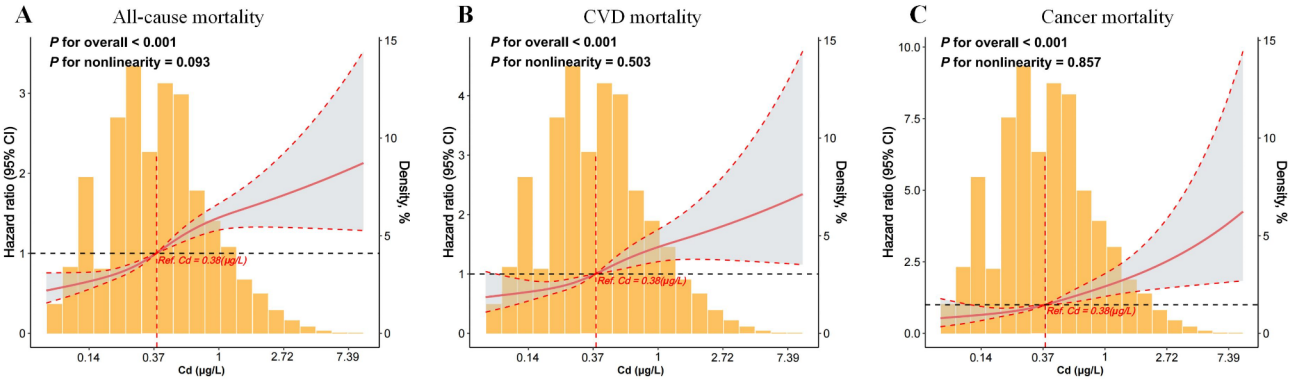


Fig. 2 Exposure-response relationships of Cd levels with **A** all-cause, **B** CVD, and **C** cancer mortality. The model was adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension

Table 3 Association of blood cd levels with oxidative stress and inflammation biomarkers

	Partially adjusted[a], β (95% CI)	*P* value	Fully adjusted[b], β (95% CI)	*P* value
Oxidative stress index				
GGT	0.059 (0.043, 0.075)	< 0.001	0.035 (0.016, 0.055)	0.001
UA	-0.009 (-0.014, -0.004)	0.001	0.011 (0.004, 0.019)	0.004
HDL	-0.003 (-0.010, 0.004)	0.351	0.012 (0.004, 0.021)	0.005
UHR	-0.001 (-0.002, 0.0005)	0.259	0.0001 (-0.001, 0.002)	0.925
Inflammatory indicators				
NLR	0.026 (0.019, 0.032)	< 0.001	0.011 (0.002, 0.020)	0.016
MLR	0.002 (-0.0003, 0.004)	0.097	0.007 (0.004, 0.010)	< 0.001
NMLR	0.024 (0.018, 0.031)	< 0.001	0.012 (0.004, 0.021)	0.005
SIRI	0.043 (0.036, 0.051)	< 0.001	0.019 (0.010, 0.029)	< 0.001
SII	0.018 (0.014, 0.023)	< 0.001	0.006 (0.0001, 0.012)	0.047

GGT, Gamma-glutamyl transferase; UA, Uric acid; HDL, High-density lipoprotein; UHR, UA to HDL ratio; NLR, Neutrophil-lymphocyte ratio; MLR, Monocyte-lymphocyte ratio; NMLR, Neutrophil-monocyte-lymphocyte ratio; SIRI, Systemic inflammation response index; SII, Systemic immune-inflammation index

[b] Trend tests were evaluated using the median of the quantile samples of blood Cd.

[c] Using ln (Cd) as a continuous variable to test the effect of per ln-unit increase in Cd on mortality.

[d] Adjusted for age, sex, and race.

[e] Adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension.

RCS (Fig. 2) indicated a trend of increasing risks for all-cause, CVD, and cancer mortality with higher blood Cd levels. The analysis did not provide significant evidence of nonlinearity (*P* for nonlinearity > 0.05).

Association of blood cd levels with oxidative stress and inflammation biomarkers

Table 3 summarizes the associations of log-transformed Cd with log-transformed oxidative stress and inflammatory biomarkers. In the fully adjusted model, Cd levels were significantly positively associated with all biomarkers except for the UHR. Specifically, blood Cd was positively associated with: GGT (β = 0.035, 95% CI: 0.016–0.055), UA (β = 0.011, 95% CI: 0.004–0.019), HDL (β = 0.012, 95% CI: 0.004–0.021), NLR (β = 0.011, 95% CI: 0.002–0.020), MLR (β = 0.007, 95% CI: 0.004–0.010), NMLR (β = 0.012, 95% CI: 0.004–0.021), SIRI (β = 0.019, 95% CI: 0.010–0.029), and SII (β = 0.006, 95% CI: 0.0001–0.012).

[a] Adjusted for age, sex, and race.

[b] Adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension.

Association of oxidative stress and inflammation biomarkers with all-cause, CVD, and cancer mortality

Table 4 presents the associations of oxidative stress and inflammation biomarkers with the risks of all-cause, CVD, and cancer mortality. In the fully adjusted models, HDL, analyzed as both a continuous and categorical variable, showed no significant association with all-cause, CVD, or cancer mortality. In contrast, higher levels of other biomarkers (UA, UHR, NLR, MLR, NMLR, SIRI, and SII) were associated with increased risks of all-cause and CVD mortality. For example, both continuous (log-transformed and standardized) and dichotomized measures (based on weighted medians) of NLR, MLR,

Table 4 Associations of oxidative stress and inflammation biomarkers with the risks of all-cause, CVD, and cancer mortality

Variable	All-cause mortality, HR (95% CI)		CVD mortality, HR (95% CI)		Cancer mortality, HR (95% CI)	
	Partially adjusted[a]	Fully adjusted[b]	Partially adjusted	Fully adjusted	Partially adjusted	Fully adjusted
Oxidative stress index						
GGT[c]	1.17 (1.12, 1.23)	1.13 (1.08, 1.19)	1.12 (1.03, 1.21)	1.07 (0.98, 1.18)	1.18 (1.06, 1.31)	1.15 (1.03, 1.28)
Below[d]	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above[d]	1.13 (1.03, 1.24)	1.09 (0.99, 1.19)	1.02 (0.88, 1.20)	0.98 (0.83, 1.16)	1.04 (0.86, 1.26)	1.00 (0.83, 1.20)
UA	1.16 (1.10, 1.22)	1.12 (1.06, 1.17)	1.25 (1.13, 1.38)	1.18 (1.08, 1.29)	0.95 (0.87, 1.05)	0.97 (0.88, 1.08)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.09 (1.00, 1.19) *	1.05 (0.96, 1.15)	1.16 (0.99, 1.35)	1.08 (0.93, 1.27)	0.86 (0.71, 1.04)	0.89 (0.73, 1.08)
HDL	0.94 (0.89, 0.99)	1.03 (0.97, 1.09)	0.96 (0.88, 1.04)	1.06 (0.96, 1.17)	0.91 (0.82, 1.01)	0.98 (0.87, 1.10)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	0.91 (0.82, 1.01)	1.05 (0.95, 1.17)	0.89 (0.75, 1.06)	1.06 (0.88, 1.26)	0.95 (0.77, 1.17)	1.08 (0.87, 1.34)
UHR	1.15 (1.10, 1.21)	1.08 (1.02, 1.13)	1.20 (1.11, 1.29)	1.09 (1.01, 1.18)	1.05 (0.95, 1.15)	1.01 (0.91, 1.12)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.15 (1.04, 1.27)	1.05 (0.95, 1.16)	1.29 (1.09, 1.52)	1.14 (0.96, 1.35)	1.01 (0.81, 1.24)	0.96 (0.76, 1.20)
Inflammatory index						
NLR	1.35 (1.29, 1.41)	1.25 (1.19, 1.31)	1.39 (1.27, 1.52)	1.28 (1.17, 1.41)	1.11 (1.01, 1.22)	1.06 (0.96, 1.16)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.43 (1.31, 1.55)	1.27 (1.16, 1.39)	1.46 (1.22, 1.75)	1.28 (1.08, 1.53)	1.10 (0.92, 1.32)	1.02 (0.85, 1.22)
MLR	1.26 (1.20, 1.33)	1.22 (1.16, 1.28)	1.30 (1.21, 1.40)	1.25 (1.17, 1.33)	0.98 (0.88, 1.08)	0.98 (0.89, 1.08)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.45 (1.32, 1.59)	1.39 (1.26, 1.53)	1.50 (1.29, 1.75)	1.41 (1.21, 1.65)	1.16 (0.93, 1.45)	1.19 (0.95, 1.49)
NMLR	1.36 (1.30, 1.43)	1.26 (1.21, 1.32)	1.40 (1.28, 1.53)	1.30 (1.18, 1.43)	1.10 (1.00, 1.21) *	1.05 (0.96, 1.16)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.48 (1.36, 1.61)	1.32 (1.20, 1.44)	1.51 (1.26, 1.80)	1.32 (1.11, 1.57)	1.05 (0.88, 1.26)	0.97 (0.81, 1.17)
SIRI	1.40 (1.34, 1.46)	1.26 (1.20, 1.33)	1.42 (1.31, 1.54)	1.28 (1.17, 1.40)	1.16 (1.06, 1.27)	1.07 (0.97, 1.18)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.66 (1.51, 1.82)	1.41 (1.28, 1.56)	1.71 (1.43, 2.06)	1.45 (1.20, 1.74)	1.31 (1.08, 1.58)	1.15 (0.94, 1.41)
SII	1.22 (1.16, 1.29)	1.15 (1.10, 1.21)	1.20 (1.09, 1.31)	1.13 (1.03, 1.24)	1.09 (1.00, 1.18)	1.02 (0.93, 1.12)
Below	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above	1.27 (1.15, 1.40)	1.14 (1.03, 1.26)	1.28 (1.06, 1.55)	1.14 (0.94, 1.39)	0.98 (0.81, 1.17)	0.89 (0.74, 1.07)

CVD mortality, Cardiovascular disease mortality; HR, Hazard ratio; GGT, Gamma-glutamyl transferase; UA, Uric acid; HDL, High-density lipoprotein; UHR, UA to HDL ratio; NLR, Neutrophil-lymphocyte ratio; MLR, Monocyte-lymphocyte ratio; NMLR, Neutrophil-monocyte-lymphocyte ratio; SIRI, Systemic inflammation response index; SII, Systemic immune-inflammation index

NMLR, and SIRI were linked to higher risks of all-cause and CVD mortality, whereas SII was primarily associated with all-cause mortality. For cancer mortality, a clear association was observed only with GGT. RCS analysis further supported the exposure-response relationships (Fig. S4).

[a] Adjusted for age, sex, and race.

[b] Adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension.

[c] Oxidative stress and inflammatory indices were used as continuous variables after logarithmic transformation and Z standardization.

[d] Cut-off values for oxidative stress and inflammatory indicators were determined by the weighted medians of the study sample.

The mediation effects of oxidative stress and inflammation biomarkers in the relationships of Cd exposure with risks of all-cause, CVD, and cancer mortality

Mediation analyses (Fig. 3, Table S5) were conducted to explore whether oxidative stress and inflammation biomarkers mediate the association between Cd exposure and mortality. For all-cause mortality, the estimated proportions of the association mediated by GGT, UA, NLR, MLR, NMLR, and SIRI were 1.8% (95% CI: 0.7–3.4%), 1.4% (95% CI: 0.3–2.7%), 2.1% (95% CI: 0.2–4.2%), 4.0% (95% CI: 2.2–6.4%), 2.6% (95% CI: 0.6–4.8%), and 3.9% (95% CI: 1.8–6.3%), respectively. For CVD mortality, the mediation proportions by UA, NLR, MLR, NMLR, and SIRI were 2.3% (95% CI: 0.5–5.3%), 2.6% (95% CI: 0.3–6.0%), 4.8% (95% CI: 2.3–9.2%), 3.2% (95% CI: 0.6–7.1%), and 4.4% (95% CI: 1.9–8.7%), respectively. For cancer mortality, GGT mediated 1.6% (95% CI: 0.1–3.8%) of the association with Cd exposure. No significant exposure-mediator interaction effects were observed (Table S6).

Fig. 3 The mediation effects of oxidative stress and inflammation biomarkers in the relationships of Cd exposure with risks of all-cause, CVD, and cancer mortality. The model was adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension

Stratified analysis

Stratified analyses by diabetes status (Fig. 4) indicated that higher Cd exposure was associated with increased risks of all-cause, CVD, and cancer mortality among both individuals with diabetes and those with prediabetes. Furthermore, we observed a significant interaction effect between blood Cd levels and diabetes status on cancer mortality (P for interaction = 0.043). In the prediabetes group, each one-unit increase in log-transformed Cd was associated with a 77% higher risk (95% CI: 41–121%), compared with a 38% higher risk (95% CI: 3–83%) in the diabetes group. However, overlapping confidence intervals suggest uncertainty regarding the magnitude of this difference. After stratification, the positive associations of oxidative stress and inflammatory biomarkers with all-cause, CVD, and cancer mortality remained robust

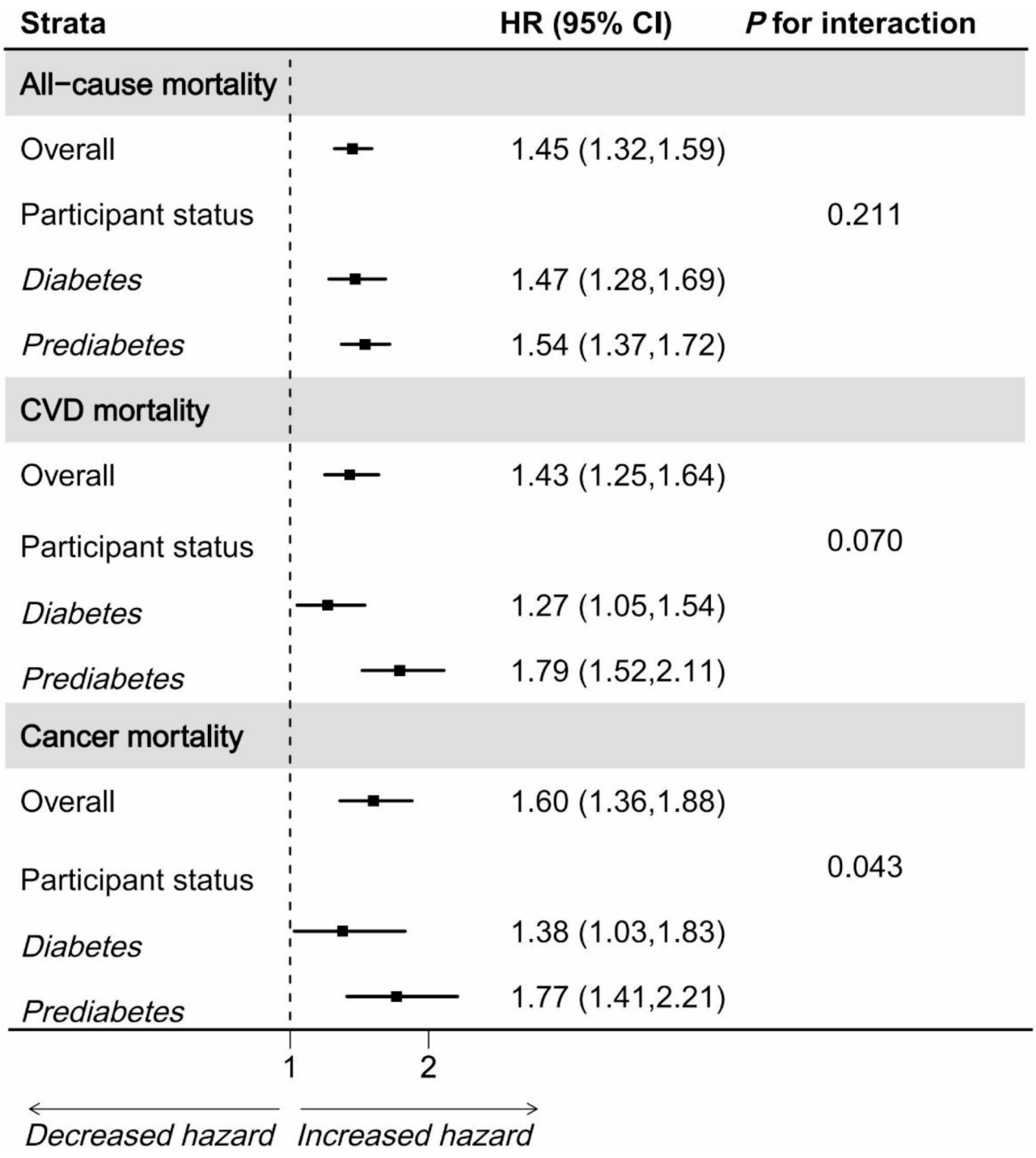


Fig. 4 Association of Cd exposure with all-cause, CVD, and cancer mortality stratified by diabetes status. The model was adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension

(Fig. 5), and the mediating effects of these biomarkers were similarly observed in both subgroups (Tables S7–S9).

After stratifying by sex, cadmium exposure was associated with an increased risk of mortality in both men and women. Compared with men, the association between blood cadmium exposure and cancer mortality appeared stronger among women (HR: 1.82, 95% CI: 1.35–2.45 vs. HR: 1.49, 95% CI: 1.24–1.80), and no significant interaction was observed (Fig. S5). In the stratified mediation analysis, the mediating effects of oxidative stress and inflammation biomarkers remained robust (Tables S10–S12).

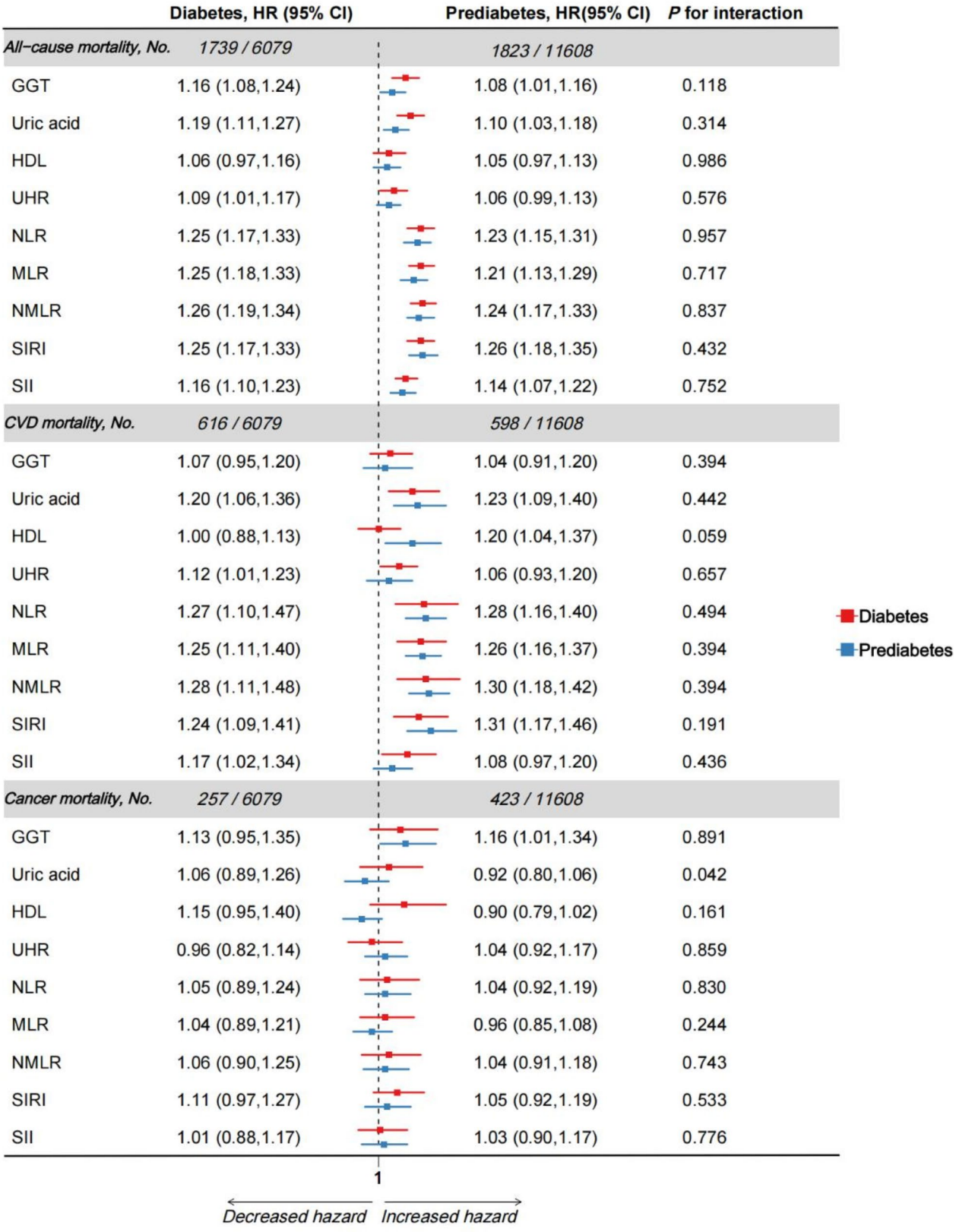


Fig. 5 Association of oxidative stress and inflammation biomarkers with all-cause, CVD, and cancer mortality risk stratified by diabetes status. The model was adjusted for age, sex, race, education level, PIR, BMI, WWI, marital status, physical activity, smoking status, alcohol status, failing kidneys, and hypertension

Sensitivity analysis

In the Fine-Gray subdistribution hazard model, the positive association between Cd exposure and both CVD and cancer mortality was maintained in univariate and multivariate analyses (Fig. S6). When neutrophil count, monocyte count, lymphocyte count, and platelet count were tested as mediating variables, only monocyte count showed a mediating effect on the association of Cd exposure with all-cause mortality (Table S13). After excluding participants who died within two years of follow-up or those with follow-up periods exceeding 15 years, the association between Cd levels and risks of all-cause, CVD, and cancer mortality remained significant (Tables S14–S17). Similarly, the re-imputation of missing values using a random forest algorithm yielded results that were consistent with our primary analyses (Tables S18 and S19). Additional adjustments for blood lead concentration or occupational factors also did not materially affect the observed associations (Tables S20–S23). Lastly, even after excluding kidney failure and hypertension from the fully adjusted model, the associations between Cd exposure and mortality risk, as well as the mediating roles of oxidative stress and inflammation biomarkers, persisted (Tables S24 and S25).

Discussion

To our knowledge, this is the first prospective cohort study to investigate the associations of blood Cd levels with the risks of all-cause, CVD, and cancer mortality in individuals with diabetes and prediabetes, while also exploring the mediating roles of oxidative stress and inflammation biomarkers. In this nationally representative cohort of U.S. adults aged 20 years and older with diabetes or prediabetes, our analyses indicated that higher blood Cd concentrations were associated with elevated mortality risks. We also observed that biomarkers of oxidative stress and inflammation could partially explain these relationships. These findings offer new insights into the impact of Cd exposure on the prognosis of individuals with diabetes, highlighting the importance of addressing environmental exposures in managing these high-risk populations.

Effects of Cd on risks of all-cause, CVD, and cancer mortality in individuals with diabetes and prediabetes

The effect of Cd exposure on mortality risk appears to be inconsistent across the general population and individuals with metabolic diseases, including diabetes. Existing studies have given limited attention to the diabetic population, and the few available studies report divergent effects of cadmium exposure on mortality risk [17–19]. Our study effectively addresses this gap, providing new insights into the relationship between cadmium exposure and mortality risk in this vulnerable group.

In this study, individuals with elevated blood Cd levels tended to exhibit higher risks of all-cause, CVD, and cancer mortality, suggesting a possible exposure–response relationship. Although our analysis did not provide statistically significant evidence of nonlinearity, the possibility of a threshold effect cannot be excluded, and further studies are needed to investigate this potential. Notably, participants with prediabetes appeared to show a somewhat greater sensitivity to elevated blood Cd levels than those with diabetes, particularly concerning cancer mortality.

Previous findings regarding Cd exposure and mortality in diabetic populations have been variable. While some studies report associations between higher Cd levels and increased all-cause mortality, they do not consistently extend to CVD or cancer mortality [43]. However, as highlighted by several recent meta-analyses, Cd exposure is strongly correlated with increased risk for CVD events [44–46]. Additionally, small sample sizes, short follow-up durations, and potential confounding factors may partly explain the heterogeneity in the literature [47]. Furthermore, existing research has largely overlooked the potential vulnerability of prediabetic individuals to Cd exposure, resulting in an underestimation of the risks faced by this population [48].

Our study provides evidence from a large-scale prospective cohort with up to 20 years of follow-up, evaluating the associations of blood Cd levels with all-cause, CVD, and cancer mortality risks in individuals with diabetes and prediabetes. Our findings indicate a trend toward increased mortality risk with higher blood Cd levels, supporting a potential exposure–response relationship. However, restricted cubic spline analysis did not demonstrate significant nonlinearity, nor did we observe any association indicating reduced risk at higher cadmium exposure levels.

In addition, it's worth noting that the risk of all-cause, CVD, and cancer mortality in individuals with prediabetes was slightly higher than that in patients with diabetes, suggesting that patients with prediabetes show greater sensitivity to Cd toxicity, especially concerning cancer mortality.

Effects of oxidative stress and inflammation on the risk of all-cause, CVD, and cancer mortality in patients with diabetes and prediabetes

We found that individuals with higher levels of certain oxidative stress and inflammation biomarkers were more likely to experience all-cause, CVD, and cancer mortality events. Most of these biomarkers demonstrated at least some evidence of a positive association with mortality outcomes, and several displayed non-linear patterns. For instance, all oxidative stress and inflammation biomarkers, except for MLR, demonstrated nonlinear

associations with all-cause mortality. Similarly, GGT, UA, HDL, UHR, and SIRI showed nonlinear relationships with CVD mortality, while GGT, NLR, NMLR, and SII exhibited nonlinear patterns for cancer mortality. Stratified and sensitivity analyses further validated the robustness of these associations.

Oxidative stress and chronic inflammation are well-recognized pathological states in diabetic patients, driven by multiple mechanisms. These include increased activation of protein kinase C (PKC) and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), reduced nitric oxide (NO) production, upregulated expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), and elevated secretion of pro-inflammatory cytokines such as TNF-α and IL-6, which are closely linked to the onset and progression of diabetes and its complications [49–51]. Especially under hyperglycemic conditions, chronic inflammatory responses exacerbate metabolic and immune dysregulation, accelerating the development of diabetes-related chronic complications [52]. Previous studies have demonstrated through both in vivo and in vitro experiments that oxidative stress and inflammatory responses significantly increase mortality risk in patients with type 2 diabetes by aggravating myocardial damage [53, 54]. For instance, diabetic mouse models lacking glutathione peroxidase-1 (Gpx1) regulatory function exhibit accelerated atherosclerosis, increased macrophage infiltration, and upregulation of inflammatory markers, highlighting the critical role of oxidative stress and inflammation in diabetes-related CVD [55].

Epidemiological evidence further supports the associations of oxidative stress and inflammation biomarkers with mortality risk. A multicenter, double-blind, placebo-controlled trial found that elevated GGT levels were significantly associated with all-cause, CVD, and cancer mortality in type 2 diabetes patients [56]. Similarly, a Korean study indicated that even moderately elevated uric acid levels were significantly related to increased risks of all-cause, CVD, and cancer mortality, even within the low-normal range [57]. Consistent with our findings, evidence from Australia demonstrated a U-shaped relationship between serum HDL levels and all-cause mortality in type 2 diabetes patients [58]. Additionally, elevated UHR levels have been strongly linked to increased risks of all-cause and CVD mortality in the general U.S. adult population [59]. Inflammatory markers derived from complete blood count indices, such as NLR and SII, have been associated with all-cause and CVD mortality risks in the general population [30, 60]. Our findings expand on this evidence by systematically examining multiple oxidative stress and inflammation markers in individuals with both diabetes and prediabetes. However, it is important to emphasize that the pattern of associations may vary by biomarker, outcome type, and population subgroup, and some of the relationships observed might not be strictly linear. These nuances reinforce the need for comprehensive assessments when evaluating the potential clinical relevance of such biomarkers in routine practice.

Mediation of oxidative stress and inflammation in the association of Cd exposure with risks of all-cause, CVD, and cancer mortality

Another significant finding of this study is that biomarkers reflecting oxidative stress and inflammation could partly mediate the association between higher blood Cd levels and mortality risk. After independently confirming the adverse effects of Cd, oxidative stress, and inflammation biomarkers on mortality risk, we further demonstrated a significant positive correlation of blood Cd levels with these biomarkers. This finding is consistent with previous studies on the relationship between cadmium and both oxidative stress and inflammatory biomarkers [61–65]. Through causal mediation analysis, we found evidence suggesting that oxidative stress biomarkers may mediate the association between blood Cd levels and the risk of all-cause, CVD, and cancer mortality in diabetic and prediabetic patients. Specifically, GGT appeared to play a potential mediating role in the association between Cd exposure and all-cause and cancer mortality, while UA seemed to primarily mediate the relationship between Cd exposure and CVD mortality. Elevated GGT levels reflect increased oxidative stress and cellular damage, which create favorable conditions for cancer initiation and progression [37], potentially amplifying the effect of Cd on cancer and all-cause mortality risk. As a pro-inflammatory factor, UA tends to form crystalline deposits on vascular walls, leading to endothelial dysfunction and promoting atherosclerosis and thrombosis [66], however, its role in cancer development remains limited [67].

For inflammation biomarkers, we found that NLR, MLR, NMLR, and SIRI significantly mediated the associations of cadmium exposure with both all-cause and CVD mortality risks. Among individual blood cell count components, only monocyte count significantly mediated the association of Cd exposure with all-cause mortality. This suggests that the impact of Cd exposure on mortality risks in individuals with diabetes and prediabetes extends beyond simple changes in immune cell counts and involves the modulation of complex immune-inflammatory response networks. These findings underscore the intricate mechanisms by which Cd exposure influences mortality risks. Additionally, stratified analyses further validated the significant and robust mediating roles of oxidative stress and inflammation biomarkers in both diabetes and prediabetes groups. However, it is

important to note that our cross-sectional study design limits the ability to establish causal relationships due to the lack of temporal precedence. Although no clear exposure–mediator interaction was observed when incorporating oxidative stress and inflammation biomarkers as interaction terms, the hypothesis of a causal relationship among cadmium exposure, oxidative stress biomarkers, and mortality risk may still lack sufficient support. Additionally, the assumption of linear relationships between the variables may not fully capture the complexity of these interactions, as non-linear relationships or threshold effects remain possible. Although we controlled for known confounders, unmeasured confounding could still bias the results and violate the assumption of independence between the mediator and the outcome. Consequently, our results should be interpreted with caution, and further cohort studies are needed to validate the robustness of the findings.

In this study, we provide novel insights into the mechanisms linking Cd exposure to increased risks of all-cause, CVD, and cancer mortality in individuals with diabetes and prediabetes. By elucidating the mediating roles of oxidative stress and inflammation, our findings enhance the understanding of the biological toxicity effects of Cd in this high-risk population and lay the groundwork for targeted interventions to mitigate the adverse health impacts of Cd exposure.

Strengths and limitations

This study possesses several notable strengths. First, we employed a large-scale prospective cohort design with a follow-up duration of up to 20 years. This design enhances the scientific rigor and validity of causal inference while improving the statistical power of the analysis. Second, we incorporated multiple oxidative stress and inflammation biomarkers, systematically evaluating their mediating roles in the relationship of Cd exposure with mortality risks in individuals with diabetes and prediabetes for the first time. This study offers deeper epidemiological insights into the adverse effects of Cd exposure, further elucidating its potential underlying mechanisms. Third, extensive stratified and sensitivity analyses were conducted to confirm the robustness and reliability of our findings.

However, this study has certain limitations. First, blood Cd concentration was used as the exposure marker, which primarily reflects recent Cd exposure rather than cumulative or long-term exposure, potentially limiting the assessment of its chronic health effects. Second, although we adjusted for a wide range of potential confounders, residual confounding remains possible due to unmeasured or uncontrolled variables, such as genetic susceptibility or co-exposure to other environmental pollutants, which could influence the observed associations. Third, due to the cross-sectional design of the NHANES, it does not allow for the assessment of changes in these variables over time, thereby limiting further investigation into their dynamic patterns. Fourth, the NHANES database does not provide specific information distinguishing between T1DM and T2DM, thus limiting our ability to separately analyze these two diabetes subtypes. Finally, this study relied on publicly available mortality data, the quality of which may be affected by follow-up duration, the accuracy of recordkeeping, and potential misclassification in cause-of-death reporting. These measurement errors could lead to non-differential misclassification bias, underestimating the exposure effect and impacting the statistical significance and causal inference derived from Cox regression models.

Conclusion

In conclusion, this large-scale longitudinal study suggests that Cd exposure is associated with increased risks of all-cause, CVD, and cancer mortality in individuals with diabetes and prediabetes. These associations may be partly explained by elevated levels of oxidative stress and inflammation biomarkers.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02698-5.

Supplementary Material 1

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Author contributions

J.L. and K.C. performed data curation, formal analysis, and visualization, and wrote the original draft. M.T., Q.M., and S.Z. contributed to validation. J.L. and X.J. supervised the project. J.L. contributed to methodology. C.W. was responsible for project administration, conceptualization, methodology, and writing– review and editing.

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Availability of data and materials

The data for this study can be accessed from the official website of the National Health and Nutrition Examination Survey at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

The NHANSE study was approved by the National Center for Health Statistics Ethics Review Board (IRB/ERB Protocol Number of each cycle was available at: https://www.cdc.gov/nchs/nhanes/about/erb.html).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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