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Association of cobalt exposure with all-cause and cardiovascular mortality in U.S. adults

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Abstract

Background Cobalt exposure is recognized as a potential risk factor for cardiovascular disease (CVD). However, the impact of cobalt exposure on mortality, particularly concerning CVD-related deaths, in the U.S. remains uncertain.

Methods Data from the National Health and Nutrition Examination Surveys (NHANES) spanning 1999–2018 were utilized to assess urinary cobalt levels in participants aged 20 years and older ($n = 15,873$). For the analysis of blood cobalt, data from NHANES covering the years 2015–2018 were considered, limited to participants aged 40 years and older ($n = 6,692$). The follow-up period extended until December 31, 2019.

Results The median values of ln-transformed urinary cobalt (creatinine corrected) and blood cobalt were − 1.10 ln(μg/g) and − 1.90 ln(μg/L), respectively. For urinary cobalt, during a median follow-up period of 130.0 months (interquartile range: 70.25–189.0), 2,304 participants died, with 613 deaths attributed to CVD. After adjusting for potential covariates, an increase in urinary cobalt level was significantly associated with a higher risk of all-cause mortality and CVD mortality (per 1 ln-unit increment, HR: 1.19, 95% CI: 1.07, 1.32; HR: 1.30, 95% CI: 1.06, 1.60, respectively). For blood cobalt, the adjusted HRs were 1.57 (95% CI: 1.15, 2.14) for all-cause mortality and 2.02 (95% CI: 1.10, 3.72) for CVD mortality.

Conclusions In the U.S., low-level environmental cobalt exposure is a significant risk factor for both all-cause mortality and CVD mortality.

Synopsis Cobalt, a metallic element commonly encountered by the general population through food, water, or air inhalation, emerges as a novel risk factor for cardiovascular disease mortality.

Keywords Cobalt, Cardiovascular disease, Mortality, NHANES

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Introduction

Cardiovascular disease (CVD) stands as the predominant cause of mortality in the United States [1]. In the year 2019 alone, an astonishing 2.81 million deaths were reported among U.S. adults aged 20 and above [2]. Notably, CVD was the underlying cause of more than 650,000 of these fatalities, constituting roughly one-fourth of the total recorded deaths [2].

Cobalt is a metallic element that non-occupationally exposed general individuals inevitably encounter in their daily lives, primarily through food consumption, water intake, or inhalation of air [3, 4]. Additionally, certain behaviors and environmental factors, such as smoking [5], vitamin B12 supplementation [6, 7], surgical procedures involving implants [7–9], and residence in industrial zones or hazardous waste sites [3], can lead to increased cobalt exposure. This heightened exposure to cobalt has been linked to various CVD, including hypertension [10–12], heart failure [13], myocardial infarct [13], and cardiomyopathy [8, 14]. The potential mechanisms underlying cobalt's cardiac toxicity involving ferroptosis, oxidative stress, lipid peroxidation, and inhibiting glutathione peroxidase 4 activity, along with DNA damage [15–17].

Indeed, limited evidence to date suggests that cobalt is not a risk factor for CVD-related mortality [18–20]. Nevertheless, these studies have certain limitations stemming from inappropriate data processing and analysis methods. These limitations include mishandling cobalt exposure variables (neglecting urine dilution correction) [19, 20], failure to simultaneously account for other confounding factors associated with CVD mortality (such as cadmium and lead) [18, 20], and the use of Poisson regression instead of COX regression, which ignores survival time [19]. Moreover, these studies relied on urinary cobalt as the indicator of cobalt exposure [18–20], which has limitations, including significant fluctuations influenced by an individual's hydration status and potential unreliability in assessing long-term cobalt exposure. In contrast, blood cobalt levels provide a more stable and reliable indicator for reflecting long-term cobalt exposure levels [7, 21]. As of now, there are no available studies that have explored the relationship between blood cobalt concentration and mortality, especially in the context of CVD mortality.

The aim of this study was to evaluate the impact of low level of environmental cobalt exposure, encompassing both blood and urine measurements, on both all-cause mortality and CVD mortality. Additionally, we calculated the burden of mortality attributable to cobalt exposure. To achieve this, we analyzed data from National Health and Nutrition Examination Survey (NHANES), a prospective and representative cohort of the U.S. general population [22].

Methods

Study design and population

NHANES is a research program aimed at evaluating the health status of both children and adults in the United States. This survey is overseen by the National Center for Health Statistics (NCHS), and its research protocol has received approval from the NCHS Institutional Review Board. All participants provide written informed consent, and the study strictly adheres to the principles outlined in the Helsinki Declaration. The NHANES interviews encompass a wide range of topics, including demographics, socioeconomic status, dietary habits, and health-related issues. The examination phase includes medical and physiological measurements, along with laboratory tests conducted by trained healthcare professionals. For more detailed information about NHANES, including its operation, design, and other pertinent details, please visit https://www.cdc.gov/nchs/nhanes/index.htm.

To investigate the relationship between cobalt exposure levels and mortality risk, we conducted a study using data from the NHANES dataset. Our study focused on two distinct aspects of cobalt exposure: urinary cobalt levels and blood cobalt levels. For the analysis of urinary cobalt, we included participants aged 20 and older from ten consecutive NHANES cycles, spanning from 1999 to 2000 to 2017–2018. This timeframe was chosen to ensure sufficient follow-up time, enhance sample size, and increase statistical power, thereby improving the reliability of our findings. Regarding cobalt levels in blood, our analysis was limited to participants aged 40 and older from two consecutive NHANES cycles, specifically from 2015 to 2016 to 2017–2018, due to the availability of blood cobalt measurements exclusively for this subgroup (Table S1). Participants were excluded if they had missing data or values exceeding the 99th percentile for cobalt exposure, incomplete mortality or follow-up time information, died within one year of their cobalt measurement, were pregnant or lactating, or had a body mass index below 18.5 kg/m^2. In the end, the analysis included a total of 15,873 participants for the evaluation of cobalt levels in urine and 6,692 participants for the assessment of cobalt levels in blood. The recruitment process is depicted in Figure S1.

Measurement of cobalt exposure

Urinary and whole blood samples were collected at mobile examination centers (MEC), processed, appropriately stored, and subsequently transported to the Laboratory Sciences Branch of the National Center for Environmental Health, Centers for Disease Control and Prevention, situated in Atlanta, Georgia, for analysis. The concentration of cobalt in both urine and whole blood samples was directly measured using inductively coupled plasma mass spectrometry. All laboratory data

underwent standardization as part of the NHANES quality assurance and quality control procedures. The limit of detection and distribution of cobalt exposure level were supplemented (see eMethod 1).

Assessment of mortality

The assessment of mortality for each participant was determined using publicly available mortality files from NHANES [23]. These files contained information on probabilistic matches between NHANES records and the National Death Index records to ascertain the vital status of each eligible NHANES participant up to December 31, 2019. Classification of underlying causes of death was based on the International Classification of Diseases, Tenth Revision (ICD-10). CVD deaths were defined by ICD-10 codes I00-I09, I11, I13, and I20-I51, while cancer deaths were defined by ICD-10 codes C00-C97. Follow-up time was calculated as the time interval from the examination date to the date of death or to December 31, 2019, whichever occurred earlier.

Other covariates

Various variables were collected via questionnaires, encompassing age, sex, race or ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other), educational attainment (grouped as college graduate or above, some college or associate's degree, and high school graduate, general educational development or less), smoking status (categorized into current, former, and never smokers), poverty income ratio (classified as <1.3, 1.3–3.49, and ≥ 3.5), dietary quality (categorized as low, moderate, and high), physical activity (categorized as inactive, insufficient, and active), alcohol consumption (categorized as none, moderate, and heavy drinking), and medical histories (including stroke, renal failure, heart failure, hypertension, and cardiovascular heart disease). At MEC, physical examinations were conducted to measure height and weight. Similar to cobalt exposure, cadmium, and lead exposure (both urine and blood levels), and serum cotinine levels were measured in the same laboratory. The definitions and details of these and other variables are provided in eMethod 2.

Statistical analysis

In all analyses of this study, sample weights, clustering, and stratification were taken into account to produce nationally representative estimates within the intricate sampling framework of NHANES [24]. For the assessment of urinary cobalt, sample weights from the urinary metals database were utilized, and for the assessment of blood cobalt, sample weights from the MEC exam were applied. The normalization of urinary heavy metal exposure levels (cobalt, lead, and cadmium) by dividing it by urinary creatinine concentration was performed to account for variations in urine dilution, ensuring that heavy metal levels were adjusted relative to the extent of urine dilution or concentration [25]. Given the right-skewed distribution of heavy metal exposure levels (both of blood and urine), a natural logarithmic transformation (base e) was applied to facilitate subsequent analysis. Participants were categorized into three groups of $<20\%$, 20 to 79.9%, and $\geq 80\%$ of ln-transformed cobalt exposure levels. The selection of cutoff values at 20% and 80% was informed by previous literature [26]. In these three groups, continuous variables were presented as weighted averages, while categorical variables were displayed as weighted percentages (WP), along with the calculation of their corresponding confidence intervals (CIs). We used the Kruskal-Wallis test to compare continuous variables and the chi-square test for categorical variables among different cobalt exposure groups.

We employed weighted Cox proportional hazards regression analysis to investigate the associations between cobalt exposure and all-cause mortality as well as mortality related to specific causes, including CVD mortality, cancer-related mortality, and mortality from other causes. We progressively adjusted our statistical models to assess potential confounding effects of various variables. The choice of covariates was informed by prior literature and their acknowledged potential to confound the associations with CVD mortality [18–20, 26, 27]. In Model 1, we adjusted for age (continuous), race, and sex. In Model 2, we further adjusted for poverty income ratio, education level, smoking status, baseline body mass index, predicted lean body mass, physical activity, Healthy Eating Index 2015 (HEI-2015) score, and alcohol consumption, in addition to the variables in Model (1) In Model 3, we extended the adjustment by including histories of hypertension, stroke, renal failure, heart failure, hypertension, and cardiovascular heart disease, as well as total cholesterol (continuous) and glycated hemoglobin (continuous) on top of the variables in Model (2) In these models, we evaluated ln-transformed cobalt exposure levels as a categorical variable and calculated the hazard ratio (HR) and its corresponding 95% CI for the high and moderate groups, with the low group as the reference. Additionally, we assessed ln-transformed cobalt exposure levels as a continuous variable and calculated the HR and corresponding 95% CI for each ln-unit increment in cobalt exposure. To examine the dose-response relationship between the ln-transformed cobalt exposure levels and mortality, we employed restricted cubic spline analysis with knots at the 10th, 50th (reference), and 90th percentiles of the ln-transformed cobalt exposure levels, and to investigate whether the relations should be judged linear. Additionally, we used Schoenfeld residuals to assess the proportionality of hazards assumption, and none of the models violated this assumption.

The population attributable fractions (PAF) was estimated to assess the proportion of mortality cases that could be prevented if participants with ln-transformed cobalt exposure levels above the 80th percentile of the distribution were reduced to levels below the 80th percentile. We used Levin's formula to calculate the PAF, consistent with prior studies [18], and applied the substitution method to estimate the corresponding 95% CI. [28] The absolute number of deaths was determined using data from the US Centers for Disease Control and Prevention Wide-ranging ONline Data for Epidemiologic Research database for the year 2019 [2].

To explore potential effect modification in the relationships between cobalt exposure levels and mortality, we performed several interaction and stratified analyses. These analyses considered factors such as age, sex, race, smoking status, educational attainment, and poverty income ratio. We calculated the p-values for the interaction with the Wald test, which can adjust for the survey design.

To ensure the robustness of our findings, we conducted several sensitivity analyses. Firstly, we utilized an alternative grouping method by categorizing participants into three groups based on tertiles of ln-transformed cobalt exposure levels. Subsequently, we examined the associations between these categories and mortality using multivariable Cox models. Secondly, to evaluate the potential confounding effects of other heavy metals known as risk factors for CVD mortality, including cadmium and lead [29], we sequentially introduced these heavy metals into the fully adjusted multivariable Cox models and assessed their impact on cobalt exposure estimates. Specifically, to evaluate urinary cobalt, we sequentially incorporated urinary cadmium and urinary lead into the fully adjusted models. For the assessment of blood cobalt, we similarly integrated blood cadmium and blood lead into the fully adjusted models. Thirdly, individuals who smoke may have higher cobalt exposure levels [5]. And serum cotinine levels reflect recent smoking behavior [30]. Therefore, we extended our analysis by incorporating serum cotinine levels into fully adjusted multivariable Cox models. Fourthly, we performed supplementary evaluations of potential confounding factors by considering different variable forms. For example, in addition to including glycated hemoglobin, we further incorporated a history of diabetes (yes/no). We also adjusted for high-density lipoprotein cholesterol (continuous) on top of total cholesterol, and in addition to accounting for a history of hypertension, we continued to adjust for both systolic and diastolic blood pressure (continuous). Fifthly, individuals with missing data across the entire dataset were excluded. Sixthly, individuals with a body mass index < 18.5 kg/m^2 were included. Finally, we selected urinary cobalt variables without creatinine correction as the indicator for urinary cobalt exposure. For each sensitivity analysis, we independently re-evaluated the associations between cobalt exposure and mortality risk using adjusted multivariable Cox models.

Missing values for variables ranged from 0.1 to 11.9%, except for blood cadmium and blood lead, which had a notably higher missing rate of 24.7% (Table S2). To address these missing values, imputation was performed using median values for numerical data and the most frequent value for categorical data. Statistical analysis was performed using R software (version 4.3.1, R Core Team, Vienna, Austria). All statistical comparisons were two-sided, and a significance level of $P < 0.05$ was used to determine statistical significance.

Results

Assessments of urinary cobalt

For assessments of cobalt in urine, the characteristics of the 15,873 participants included in the study are summarized in Table 1. Their weighted mean age was 47.1 (95% CI: 46.6, 47.6) years, with 7,893 being female (WP, 50.9%, 95% CI: 49.9%, 51.8%). Participants with higher urinary cobalt levels tended to be older, female, have a lower body mass index, be non-drinkers, have lower total cholesterol, have a higher HEI-2015 score, were more likely to have a history of stroke, heart failure, and cardiovascular heart disease, and had higher levels of urinary cadmium and urinary lead (all $P < 0.05$).

During a median follow-up period of 130.0 months (interquartile range: 70.25–189.0), 2,304 participants died, of whom 613 deaths were attributed to CVD, 527 to cancer, and 1,164 to other causes. After adjusting for potential covariates, participants in the high urinary cobalt group exhibited a significantly increased risk of all-cause mortality (HR: 1.26, 95% CI: 1.05, 1.52) and CVD mortality (HR: 1.67, 95% CI: 1.15, 2.44) compared to the low group. There was no significant difference between the moderate and low groups for these endpoints (Table 2). Additionally, models were also developed using ln-transformed urinary cobalt as a continuous covariate, and adjusted HRs and 95% CIs were calculated for all-cause mortality and CVD mortality: Per 1 ln-unit increment, HR: 1.19 (95% CI: 1.07, 1.32), and 1.30 (95% CI: 1.06, 1.60), respectively (Table 2). Figure 1 illustrates the dose-response relationship between ln-transformed urinary cobalt levels and the risk of all-cause and CVD mortality. For all-cause mortality, a nonlinear J-shaped association was observed (P-nonlinearity < 0.001), while for CVD mortality, a linear relationship was evident (P-nonlinearity > 0.05).

The adjusted PAF for participants with ln-transformed urinary cobalt levels above the 80th percentile, compared to those with low or intermediate levels (< 80th percentile), for all-cause mortality, and CVD mortality

Table 1 Survey-weighted baseline characteristics of the study participants by ln-transformed corrected Cobalt in urine, NHANES 1999–2018

Characteristic	*N*	Overall, *N* = 15,873 (100%)	Low, *N* = 3396, WP = 20.2% (95%CI: 19.1%, 21.3%)	Moderate, *N* = 9437, WP = 60.5% (95%CI: 59.4%, 61.6%)	High, *N* = 3040, WP = 19.3% (95%CI: 18.4%, 20.1%)	*P* Value
Age, **years**	-	47.1 (46.6, 47.6)	43.7 (43.0, 44.3)	47.5 (46.9, 48.1)	49.3 (48.4, 50.2)	< 0.001
Sex, **%**						< 0.001
Female	7,893	50.9% (49.9%, 51.8%)	25.8% (24.1%, 27.7%)	50.2% (48.9%, 51.5%)	79.2% (77.0%, 81.2%)	
Male	7,980	49.1% (48.2%, 50.1%)	74.2% (72.3%, 75.9%)	49.8% (48.5%, 51.1%)	20.8% (18.8%, 23.0%)	
Race, **%**						< 0.001
Non-Hispanic White	6,878	68.3% (66.1%, 70.5%)	61.1% (57.9%, 64.3%)	70.2% (67.9%, 72.3%)	70.1% (67.2%, 72.9%)	
Non-Hispanic Black	3,352	11.2% (10.1%, 12.4%)	20.9% (18.6%, 23.4%)	9.2% (8.3%, 10.3%)	7.2% (6.2%, 8.3%)	
Hispanic	1,344	5.7% (4.8%, 6.7%)	5.8% (4.6%, 7.3%)	5.5% (4.7%, 6.5%)	6.1% (4.7%, 7.8%)	
Other	4,299	14.8% (13.4%, 16.2%)	12.2% (10.6%, 13.9%)	15.1% (13.6%, 16.6%)	16.6% (14.7%, 18.7%)	
Education levels, **%**						0.26
High school graduate/GED or less	8,079	42.2% (40.6%, 43.8%)	42.5% (40.0%, 45.0%)	42.6% (40.8%, 44.5%)	40.6% (37.9%, 43.3%)	
Some college or associate's degree	4,435	30.5% (29.5%, 31.5%)	31.7% (29.6%, 33.9%)	30.1% (28.9%, 31.2%)	30.6% (28.4%, 33.0%)	
College graduate or above	3,359	27.3% (25.7%, 28.9%)	25.8% (23.6%, 28.2%)	27.3% (25.5%, 29.2%)	28.8% (26.4%, 31.3%)	
Poverty income ratio, **%**						0.004
Low (< 1.3)	4,390	19.7% (18.6%, 20.9%)	18.6% (17.0%, 20.4%)	19.2% (18.0%, 20.5%)	22.5% (20.6%, 24.4%)	
Middle (1.3 to < 3.5)	6,973	40.9% (39.6%, 42.2%)	40.4% (38.0%, 42.8%)	40.9% (39.4%, 42.5%)	41.3% (39.1%, 43.6%)	
High (> = 3.5)	4,510	39.4% (37.7%, 41.1%)	41.0% (38.3%, 43.8%)	39.9% (37.9%, 41.8%)	36.2% (33.6%, 38.9%)	
Body mass index, **kg/m^2**						< 0.001
Normal (< 25)	4,469	29.6% (28.4%, 30.7%)	23.9% (22.0%, 26.0%)	30.3% (28.9%, 31.7%)	33.3% (31.2%, 35.6%)	
Overweight (25 to < 30)	5,679	35.3% (34.2%, 36.5%)	36.2% (33.8%, 38.8%)	35.3% (33.9%, 36.7%)	34.5% (32.4%, 36.6%)	
Obese (30 or greater)	5,725	35.1% (33.9%, 36.3%)	39.8% (37.4%, 42.3%)	34.4% (33.0%, 35.9%)	32.2% (30.2%, 34.3%)	
Lean body mass, **kg**						< 0.001
Low (1st tertile)	4,978	27.9% (26.9%, 28.8%)	13.6% (12.2%, 15.0%)	27.9% (26.6%, 29.2%)	42.8% (40.7%, 44.9%)	
Moderate (2nd tertile)	5,877	36.6% (35.6%, 37.6%)	34.9% (32.8%, 37.0%)	37.3% (35.9%, 38.6%)	36.0% (33.9%, 38.2%)	
High (3rd tertile)	5,018	35.6% (34.5%, 36.7%)	51.6% (49.2%, 54.0%)	34.8% (33.5%, 36.2%)	21.2% (19.2%, 23.3%)	
Alcohol intake, **%**						< 0.001
None	12,114	72.4% (71.0%, 73.6%)	68.0% (65.8%, 70.2%)	71.8% (70.2%, 73.4%)	78.6% (76.3%, 80.7%)	
Moderate	1,423	9.6% (9.0%, 10.2%)	10.6% (9.3%, 12.1%)	10.0% (9.3%, 10.8%)	7.2% (6.0%, 8.6%)	
Heavy	2,336	18.1% (17.0%, 19.1%)	21.3% (19.5%, 23.3%)	18.2% (16.9%, 19.5%)	14.2% (12.4%, 16.3%)	
Smoking status, **%**						0.38
Current	3,273	21.3% (20.3%, 22.3%)	22.3% (20.4%, 24.2%)	21.3% (20.0%, 22.6%)	20.2% (18.4%, 22.1%)	
Former	4,003	25.4% (24.4%, 26.5%)	24.3% (22.3%, 26.3%)	26.0% (24.7%, 27.3%)	25.0% (22.4%, 27.8%)	
Never	8,597	53.3% (52.1%, 54.5%)	53.5% (51.1%, 55.8%)	52.8% (51.1%, 54.4%)	54.9% (52.1%, 57.6%)	
Ln-transformed serum cotinine (ng/mL), **%**						< 0.001
Low (1st tertile)	5,027	32.9% (31.4%, 34.4%)	25.1% (22.7%, 27.5%)	33.5% (31.8%, 35.2%)	39.2% (36.8%, 41.7%)	
Moderate (2nd tertile)	5,847	34.8% (33.8%, 35.9%)	36.3% (34.2%, 38.4%)	35.0% (33.6%, 36.5%)	32.7% (30.7%, 34.9%)	
High (3rd tertile)	4,999	32.3% (31.1%, 33.5%)	38.7% (36.2%, 41.2%)	31.5% (30.2%, 32.9%)	28.1% (25.9%, 30.4%)	
Physical activity, **%**						< 0.001
Inactive	3,786	18.8% (17.9%, 19.8%)	15.2% (13.6%, 16.8%)	18.7% (17.6%, 19.9%)	22.9% (20.8%, 25.2%)	
Insufficient	2,832	17.7% (16.9%, 18.5%)	18.7% (17.1%, 20.4%)	17.3% (16.3%, 18.5%)	17.7% (15.8%, 19.8%)	
Active	9,255	63.5% (62.3%, 64.7%)	66.2% (64.2%, 68.1%)	63.9% (62.4%, 65.4%)	59.4% (56.9%, 61.9%)	
Healthy Eating Index–2015 score, **%**						< 0.001
Low (1st tertile)	4,942	32.7% (31.4%, 33.9%)	35.8% (33.5%, 38.1%)	32.1% (30.7%, 33.6%)	31.0% (28.8%, 33.4%)	
Moderate (2nd tertile)	6,033	37.6% (36.5%, 38.7%)	39.2% (36.9%, 41.5%)	37.5% (36.4%, 38.7%)	36.1% (33.7%, 38.7%)	
High (3rd tertile)	4,898	29.7% (28.6%, 30.9%)	25.1% (23.4%, 26.8%)	30.3% (28.9%, 31.8%)	32.8% (30.6%, 35.1%)	
Stroke, **%**						0.016
Non	15,272	97.4% (97.1%, 97.7%)	97.8% (97.3%, 98.3%)	97.5% (97.1%, 97.9%)	96.6% (95.8%, 97.3%)	
Yes	601	2.6% (2.3%, 2.9%)	2.2% (1.7%, 2.7%)	2.5% (2.1%, 2.9%)	3.4% (2.7%, 4.2%)	

Table 1 (continued)

Characteristic	N	Overall, N = 15,873 (100%)	Low, N = 3396, WP = 20.2% (95%CI: 19.1%, 21.3%)	Moderate, N = 9437, WP = 60.5% (95%CI: 59.4%, 61.6%)	High, N = 3040, WP = 19.3% (95%CI: 18.4%, 20.1%)	P Value
Heart failure, %						< 0.001
Non	15,407	97.9% (97.5%, 98.1%)	98.4% (97.8%, 98.8%)	98.0% (97.6%, 98.3%)	96.9% (96.1%, 97.5%)	
Yes	466	2.1% (1.9%, 2.5%)	1.6% (1.2%, 2.2%)	2.0% (1.7%, 2.4%)	3.1% (2.5%, 3.9%)	
Cardiovascular heart disease, %						< 0.001
Non	15,246	96.6% (96.2%, 97.1%)	97.7% (97.0%, 98.2%)	96.7% (96.1%, 97.2%)	95.4% (94.3%, 96.3%)	
Yes	627	3.4% (2.9%, 3.8%)	2.3% (1.8%, 3.0%)	3.3% (2.8%, 3.9%)	4.6% (3.7%, 5.7%)	
Renal failure, %						0.57
Non	15,393	97.5% (97.1%, 97.8%)	97.6% (96.8%, 98.1%)	97.6% (97.2%, 98.0%)	97.2% (96.3%, 97.9%)	
Yes	480	2.5% (2.2%, 2.9%)	2.4% (1.9%, 3.2%)	2.4% (2.0%, 2.8%)	2.8% (2.1%, 3.7%)	
Hypertension, %						0.16
Non	10,279	69.6% (68.4%, 70.7%)	71.0% (68.7%, 73.1%)	69.6% (68.3%, 70.9%)	68.1% (65.7%, 70.4%)	
Yes	5,594	30.4% (29.3%, 31.6%)	29.0% (26.9%, 31.3%)	30.4% (29.1%, 31.7%)	31.9% (29.6%, 34.3%)	
Systolic blood pressure, mmHg	-	123.0 (122.6, 123.4)	122.8 (122.0, 123.6)	122.9 (122.4, 123.4)	123.5 (122.7, 124.3)	0.68
Diastolic blood pressure, mmHg	-	71.3 (71.0, 71.7)	72.8 (72.2, 73.3)	71.1 (70.7, 71.6)	70.5 (69.9, 71.0)	< 0.001
Diabetes mellitus, %						0.10
Non	13,915	91.2% (90.7%, 91.7%)	92.0% (91.0%, 92.9%)	91.2% (90.5%, 91.9%)	90.2% (88.7%, 91.4%)	
Yes	1,958	8.8% (8.3%, 9.3%)	8.0% (7.1%, 9.0%)	8.8% (8.1%, 9.5%)	9.8% (8.6%, 11.3%)	
Glycosylated hemoglobin, %	-	5.6 (5.6, 5.6)	5.5 (5.5, 5.6)	5.6 (5.6, 5.6)	5.6 (5.6, 5.6)	0.007
Total cholesterol, mg/dL	-	196.1 (195.2, 197.1)	196.3 (194.2, 198.3)	196.8 (195.7, 197.9)	193.9 (192.0, 195.7)	0.003
High-density lipoprotein cholesterol, mg/dL	-	52.9 (52.5, 53.3)	49.6 (48.9, 50.3)	52.7 (52.2, 53.2)	56.9 (56.1, 57.6)	< 0.001
Ln-transformed corrected cadmium in urine*, ln(μg/g)	-	-1.5 (-1.5, -1.4)	-1.7 (-1.8, -1.7)	-1.5 (-1.5, -1.4)	-1.2 (-1.3, -1.2)	< 0.001
Ln-transformed corrected lead in urine*, ln(μg/g)	-	-0.6 (-0.6, -0.6)	-0.9 (-0.9, -0.8)	-0.6 (-0.6, -0.6)	-0.4 (-0.4, -0.4)	< 0.001

* Cobalt, cadmium, and lead levels in urine (measured in μg/L) were ln-transformed after correcting for urinary creatinine levels (measured in g/L)

The data were presented as weighted percentages or means (with 95% confidence intervals), and the absolute numbers represent unweighted observed values. Participants were categorized into three groups based on ln-transformed corrected urinary cobalt levels: <20% (-1.57 ln(μg/g)), 20 to 79.9%, and ≥ 80% (-0.57 ln(μg/g)). CI: confidence interval; GED: general educational development; WP: weighted percentage

were 5.5% (95% CI: 2.1%, 9.1%), and 9.5% (95% CI: 3.4%, 16.5%), respectively. This corresponds to an estimated 154,000 (95% CI: 60,000 to 256,000) all-cause deaths, and 63,000 (95% CI: 22,000 to 108,000) CVD deaths among individuals aged 20 and older in the year 2019 (Table 2).

Assessments of blood Cobalt

For assessments of cobalt in blood, the characteristics of the 6,692 participants included in the study are summarized in Table S3. Their weighted mean age was 58.6 (95% CI: 57.9, 59.3) years, with 3,470 being female (WP, 52.7%, 95% CI: 51.3%, 54.1%). Participants with higher blood cobalt levels tended to be older, female, have a lower body mass index, have lower total cholesterol, were more likely to have a history of stroke, and heart failure, and had a higher level of blood cadmium (all $P < 0.05$).

During a median follow-up period of 36.0 months (interquartile range: 23.8–49.0), 206 participants died, of whom 48 deaths were attributed to CVD, 48 to cancer, and 110 to other causes. After adjusting for potential covariates, participants in the high blood cobalt group exhibited a significantly increased risk of all-cause mortality (HR: 2.20, 95% CI: 1.54, 3.15), and CVD mortality (HR: 2.37, 95% CI: 1.04, 5.40) compared to the low group. There was no significant difference between the moderate and low groups for these endpoints (Table 3). Additionally, models were also constructed using ln-transformed blood cobalt as a continuous covariate, and adjusted HRs and 95% CIs were calculated for all-cause mortality, and CVD mortality: Per 1 ln-unit increment, HR: 1.57 (95% CI: 1.15, 2.14), and 2.02 (95% CI: 1.10, 3.72), respectively (Table 3). Figure 1 illustrates the dose-response relationship between ln-transformed blood cobalt levels and the risk of all-cause and CVD mortality, all showing a linear correlation (P-nonlinearity > 0.05).

The adjusted PAFs for participants with ln-transformed blood cobalt levels above the 80th percentile, compared to those with low or intermediate levels (< 80th percentile), for all-cause mortality, and CVD mortality were 12.8% (95% CI: 2.5%, 25.3%), and 17.1% (95% CI: 1.6%, 36.7%), respectively. This corresponds to an estimated 346,000 (95% CI: 66,000 to 683,000) all-cause deaths, and 135,000 (95% CI: 39,000 to 248,000) CVD deaths among individuals aged 40 and older in the year 2019 (Table 3).

Table 2 Adjusted hazards ratios for the relationship between ln-transformed corrected Cobalt in urine and the risk of mortality, NHANES 1999–2018

	Ln-transformed corrected cobalt in urine, HR (95% CI)					Population attributable fraction (95% CI)	Avoidable deaths (95% CI)
	Low (< 20%)	Moderate (20-79.9%)	High (≥ 80%)	*P* for trend	Per 1 ln-unit increment		
All-cause mortality							
Deaths, No.	478	1339	487				
Model 1	1 (reference)	1.00 (0.87, 1.15)	1.40 (1.17, 1.68)	< 0.001	1.29 (1.17, 1.42)		
Model 2	1 (reference)	0.98 (0.85, 1.13)	1.32 (1.09, 1.60)	0.005	1.24 (1.13, 1.37)		
Model 3	1 (reference)	0.96 (0.83, 1.11)	1.26 (1.05, 1.52)	0.014	1.19 (1.07, 1.32)	5.5% (2.1%, 9.1%)	154,000 (60,000 to 256,000)
Cardiovascular disease mortality							
Deaths, No.	121	346	146				
Model 1	1 (reference)	1.17 (0.88, 1.56)	1.89 (1.35, 2.65)	< 0.001	1.46 (1.23, 1.75)		
Model 2	1 (reference)	1.19 (0.90, 1.57)	1.87 (1.32, 2.64)	< 0.001	1.44 (1.21, 1.72)		
Model 3	1 (reference)	1.16 (0.86, 1.57)	1.67 (1.15, 2.44)	0.003	1.30 (1.06, 1.60)	9.5% (3.4%, 16.5%)	63,000 (22,000 to 108,000)
Cancer mortality							
Deaths, No.	104	333	90				
Model 1	1 (reference)	1.20 (0.91, 1.57)	1.30 (0.91, 1.87)	0.15	1.19 (0.99, 1.44)		
Model 2	1 (reference)	1.15 (0.87, 1.52)	1.18 (0.82, 1.71)	0.37	1.13 (0.93, 1.37)		
Model 3	1 (reference)	1.18 (0.89, 1.56)	1.21 (0.84, 1.73)	0.37	1.14 (0.94, 1.38)	1.1% (-4.1%, 7.2%)	7,000 (-24,000 to 43,000)
Other mortality							
Deaths, No.	253	660	251				
Model 1	1 (reference)	0.86 (0.71, 1.03)	1.25 (0.96, 1.61)	0.10	1.25 (1.07, 1.46)		
Model 2	1 (reference)	0.84 (0.70, 1.00)	1.17 (0.90, 1.52)	0.24	1.21 (1.04, 1.40)		
Model 3	1 (reference)	0.81 (0.67, 0.97)	1.12 (0.87, 1.45)	0.37	1.16 (0.99, 1.36)	5.5% (1.0%, 10.6%)	86,000 (16,000 to 166,000)

In Model 1, we adjusted for age (continuous), race, and sex. In Model 2, we further adjusted for poverty income ratio, education level, smoking status, baseline body mass index, predicted lean body mass, physical activity, HEI-2015 score, and alcohol consumption, in addition to the variables in Model (1) In Model 3, we extended the adjustment by including histories of stroke, heart failure, renal failure, hypertension, and cardiovascular heart disease, as well as total cholesterol (continuous) and glycated hemoglobin (continuous) on top of the variables in Model (2) All of the models satisfied the proportionality of hazards assumption. CI: confidence interval; HR: hazards ratios

Stratified analysis

Significant interactions were observed between ln-transformed urinary cobalt and race concerning all-cause mortality and CVD mortality. The association between ln-transformed urinary cobalt and all-cause mortality and CVD mortality remained significant among non-Hispanic White individuals (Per 1 ln-unit increment, HR for all-cause mortality: 1.18, 95% CI: 1.08, 1.29; HR for CVD mortality: 1.35, 95% CI: 1.13, 1.61), whereas it was not significant for individuals of non-Hispanic Black (P for interaction < 0.05). No significant interactions were observed for other covariates (Table S4).

Sensitivity analysis

We performed sensitivity analyses using an alternative grouping method based on tertiles. These analyses consistently supported our initial findings, showing that individuals with higher cobalt exposure levels had a greater risk of all-cause or CVD mortality when compared to those with lower levels (Table S5). When we incorporated ln-transformed cadmium exposure (continuous), ln-transformed lead exposure (continuous), ln-transformed serum cotinine levels, diabetes (yes/no), both high-density lipoprotein cholesterol (continuous) and total cholesterol, or both systolic and diastolic blood pressure (continuous) into our primary model, there was no significant attenuation in the estimates for ln-transformed cobalt exposure. Excluding individuals with missing data across the entire dataset or including participants with a body mass index < 18.5 kg/m^2 did not alter the HR point estimates for ln-transformed cobalt exposure (Table S6).

However, when we used urinary cobalt variables without creatinine correction, we found no significant associations with either all-cause or CVD mortality. These findings diverge from the primary analysis, which utilized urinary cobalt variables corrected for creatinine (Table S7).

Discussion

To our knowledge, this study is the first and largest investigation into the relationship between cobalt exposure (measured in both blood and urine) and the risk of all-cause mortality and CVD mortality. Our analysis of a nationally representative cohort of U.S. adults

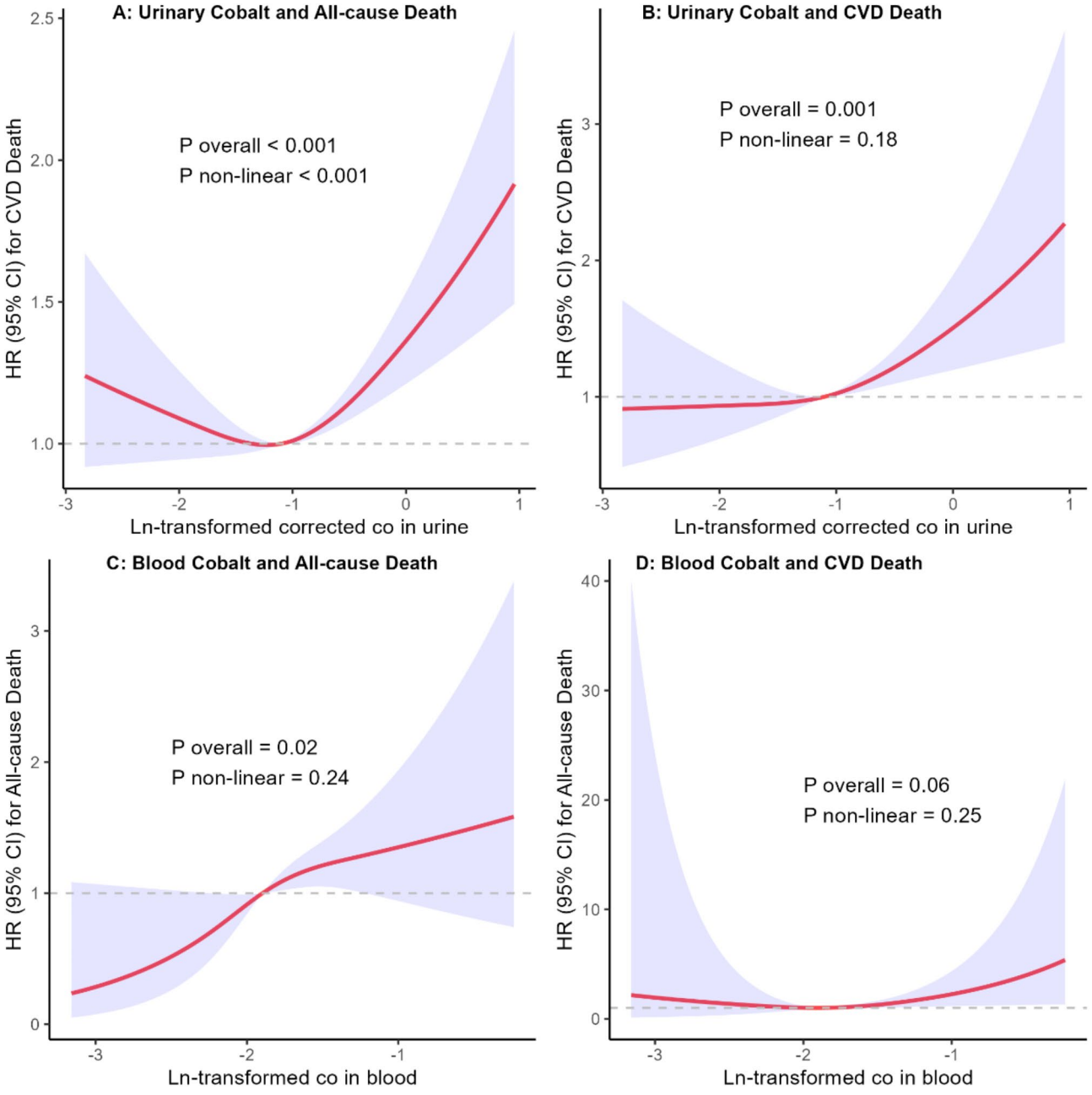

Fig. 1 Dose-response relationships between cobalt exposure and mortality using restricted cubic splines. **A**, Urinary cobalt and all-cause mortality; **B**, Urinary cobalt and CVD mortality; **C**, Blood cobalt and all-cause mortality; **D**, Blood cobalt and CVD mortality. The analyses utilized COX models with restricted cubic splines. Hazard ratios (HRs) were calculated using NHANES survey weights. The reference point was set at the weighted median value of cobalt exposure [-1.10 ln(μg/g) for urinary cobalt; and – 1.90 ln(μg/L) for blood cobalt]. Solid lines represent HRs, and the lightly shaded areas indicate 95% CIs. Abbreviations: CI: Confidence interval; Co: Cobalt; CVD: Cardiovascular disease; HR: Hazard ratio

consistently revealed significant associations between cobalt exposure and both all-cause and CVD mortality, even after rigorous multivariate adjustments and sensitivity analyses. Importantly, our estimates indicate that a substantial number of deaths, especially those related to CVD, can be attributed to cobalt exposure. These findings underscore the significant, yet often overlooked, role of low-level cobalt exposure as a risk factor for mortality in the U.S. general population.

Our findings regarding urinary cobalt differ from previous research to some extent. For instance, one study that used NHANES data from 1999 to 2014 identified an association between urinary cobalt concentration and all-cause mortality, although it found only a marginal, statistically nonsignificant association with CVD

Table 3 Adjusted hazards ratios for the relationship between ln-transformed Cobalt in blood and the risk of mortality, NHANES 2015–2018

	Ln-transformed cobalt in blood, HR (95% CI)					Population attributable fraction (95% CI)	Avoidable deaths (95% CI)
	Low (< 20%)	Moderate (20-79.9%)	High (≥ 80%)	*P* for trend	Per 1 ln-unit increment		
All-cause mortality							
Deaths, No.	43	94	69				
Model 1	1 (reference)	1.45 (0.84, 2.51)	2.63 (1.83, 3.78)	< 0.001	1.75 (1.37, 2.25)		
Model 2	1 (reference)	1.33 (0.78, 2.26)	2.27 (1.53, 3.37)	< 0.001	1.60 (1.14, 2.23)		
Model 3	1 (reference)	1.34 (0.75, 2.38)	2.20 (1.54, 3.15)	< 0.001	1.57 (1.15, 2.14)	12.8% (2.5%, 25.3%)	346,000 (66,000 to 683,000)
Cardiovascular disease mortality							
Deaths, No.	10	18	20				
Model 1	1 (reference)	1.20 (0.41, 3.53)	2.78 (1.19, 6.50)	0.02	1.92 (1.13, 3.26)		
Model 2	1 (reference)	1.03 (0.38, 2.82)	2.53 (1.08, 5.90)	0.03	2.10 (1.22, 3.62)		
Model 3	1 (reference)	1.01 (0.40, 2.57)	2.37 (1.04, 5.40)	0.04	2.02 (1.10, 3.72)	20.8% (6.0%, 38.1%)	135,000 (39,000 to 248,000)
Cancer mortality							
Deaths, No.	13	22	13				
Model 1	1 (reference)	1.50 (0.48, 4.68)	2.40 (0.90, 6.41)	0.08	1.58 (1.06, 2.34)		
Model 2	1 (reference)	1.46 (0.46, 4.63)	2.15 (0.71, 6.46)	0.17	1.40 (0.76, 2.57)		
Model 3	1 (reference)	1.45 (0.43, 4.90)	1.92 (0.68, 5.41)	0.21	1.25 (0.77, 2.05)	8.6% (-12.0%, 44.8%)	51,000 (-71,000 to 264,000)
Other mortality							
Deaths, No.	20	54	36				
Model 1	1 (reference)	1.59 (0.77, 3.26)	2.80 (1.23, 6.37)	0.01	1.73 (1.19, 2.53)		
Model 2	1 (reference)	1.46 (0.72, 2.95)	2.40 (1.04, 5.52)	0.04	1.51 (0.95, 2.39)		
Model 3	1 (reference)	1.46 (0.73, 2.93)	2.28 (0.98, 5.29)	0.05	1.46 (0.92, 2.32)	12.0% (1.2%, 25.3%)	175,000 (17,000 to 369,000)

In Model 1, we adjusted for age (continuous), race, and sex. In Model 2, we further adjusted for poverty income ratio, education level, smoking status, baseline body mass index, predicted lean body mass, physical activity, HEI-2015 score, and alcohol consumption, in addition to the variables in Model (1) In Model 3, we extended the adjustment by including histories of stroke, heart failure, renal failure, hypertension, and cardiovascular heart disease, as well as total cholesterol (continuous) and glycated hemoglobin (continuous) on top of the variables in Model (2) All of the models satisfied the proportionality of hazards assumption. CI: confidence interval; HR: hazards ratios

mortality [18]. Conversely, another study, also based on NHANES data from the same period, did not report a significant association between urinary cobalt concentration and either all-cause or CVD mortality [19]. Additionally, a study using NHANES data from 2011 to 2016 suggested that elevated urinary cobalt concentration was not linked to increased all-cause mortality rates (P for trend = 0.769); however, it did not investigate CVD mortality [20]. The inconsistencies in previous study findings can be attributed to several factors, including variations in the handling of urinary creatinine levels during cobalt analysis. The adjustment of urinary cobalt levels for urinary creatinine concentrations helps eliminate variations due to urine dilution or concentration, thereby enhancing the comparability and accuracy of the results [25]. For example, Fan et al. applied creatinine correction to urinary cobalt levels [18], while Duan et al. utilized uncorrected urinary cobalt levels but included creatinine adjustments in their models [19]. In contrast, Zhao et al. did not account for the influence of creatinine at all [20]. Our sensitivity analysis also suggests that the correlation between urinary cobalt and mortality may be influenced by urinary creatinine. Besides, differences in data analysis methods, such as the use of COX regression [18, 20] and Poisson regression [19], the exclusion of specific NHANES datasets (e.g., 2015-2018[18, 19] or 1999-2010[20]), and the omission of simultaneous adjustments for potential heavy metal variables associated with CVD mortality [18, 20], like cadmium and lead, can also concluded different results. In our study, we aimed to address these limitations by incorporating the most recent and complete NHANES data, conducting rigorous multivariate adjustments, performing multiple sensitivity analyses, and analyzing creatinine-corrected urinary cobalt. These efforts enabled us to derive more robust conclusions regarding its association with mortality.

We present, for the first time, evidence of a significant association between blood cobalt levels and both all-cause and CVD mortality. In comparison to urinary cobalt, whole blood is identified as the superior matrix for assessment. This preference is rooted in the fact that cobalt concentrations in urine samples tend to exhibit

greater variability, influenced by the patient's hydration status, and have faster excretion kinetics, primarily suitable for monitoring recent exposure levels. In contrast, blood cobalt levels offer a more stable indicator and are better suited to reflect long-term cobalt exposure levels [7, 21]. The fluctuations in urinary cobalt levels may introduce non-differential measurement errors, potentially biasing estimates towards zero in urinary cobalt models. For example, Fan et al. observed only a marginal and statistically nonsignificant association between urinary cobalt concentration and CVD mortality [18], implying that the risk linked to cobalt exposure may have been underestimated when focusing solely on urinary cobalt levels. Our data further substantiates this notion, as both biomarkers (urinary cobalt and blood cobalt) exhibit correlations with all-cause and CVD mortality, with a stronger association observed for blood cobalt. However, it is essential to exercise caution when interpreting our findings regarding blood cobalt and CVD mortality. The availability of blood cobalt data is limited to the most recent NHANES dataset from 2015 to 2018, and the follow-up period only extends until December 31, 2019, resulting in a relatively short follow-up duration and a smaller number of observed CVD-related events. This implies that our results require further confirmation through larger-scale and longer follow-up studies. Nonetheless, our findings align with previous research indicating that cobalt exposure has been associated with various CVD, including hypertension [10–12], heart failure [13], myocardial infarct [13], and cardiomyopathy [8, 14].

Exposure to cobalt can lead to CVD through the induction of ferroptosis, a process that involves an increase in lipid peroxides and lipid-related radicals, resulting in cell death [15]. Cobalt can enter the bloodstream and reach the heart, where it induces a ferroptosis-like cell death by enhancing intracellular reactive oxygen species levels, increasing cytoplasmic Fe^{2+} levels, promoting lipid peroxidation, and inhibiting glutathione peroxidase 4 activity. These mechanisms contribute to multi-system toxicity symptoms, including CVD [16]. Additionally, cobalt can cause CVD by inducing single-strand breaks in DNA and inhibiting nucleotide excision DNA repair, potentially augmenting DNA damage caused by other agents and leading to genomic instability and cellular dysfunction [17].

Our study has several limitations. Firstly, it is an observational cohort study, and thus, causal inferences cannot be drawn. Secondly, we only have data on cobalt exposure at a single time point, which may underestimate the association between cobalt exposure and mortality due to non-differential measurement errors. Thirdly, despite extensive adjustments for multiple covariates, it's important to acknowledge that unmeasured and residual confounding factors, like air pollution and arsenic, established risk factors for CVD mortality [29], could potentially exert an influence on our findings. Fourthly, the causes of death in this study were obtained from death certificates, which might be subject to coding errors. Fifthly, the analysis of blood cobalt is limited by the relatively small number of CVD-related deaths in this study, potentially affecting result reliability, necessitating further confirmation through larger-scale research. Finally, it's important to note that blood cobalt measurements were specifically conducted on individuals aged 40 and older, which means that the results for blood cobalt may not be applicable to adults aged 20 to 39 in the United States.

Conclusions

Our findings emphasize that low-level environmental cobalt exposure represents a significant risk factor for mortality in the U.S., particularly in the context of CVD deaths. However, this risk associated with cobalt exposure has been ignored all along, despite the fact that every individual inevitably encounters cobalt in their daily life. Reducing cobalt exposure levels could potentially prevent a substantial number of CVD deaths. These research findings underscore new perspectives critical for developing comprehensive strategies to prevent CVD-related deaths.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22753-w.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualization: Fuwei Xing, Chunhui He, Min Gao, and Ting He. Methodology: Fuwei Xing, Min Gao. Software: Fuwei Xing and Min Gao. Validation: Chunhui He. Formal analysis: Fuwei Xing and Min Gao. Obtained funding: Ting He. Writing-original draft preparation: Fuwei Xing. Writing-review and editing: Chunhui He, Min Gao, and Ting He. Fuwei Xing and Chunhui He have directly accessed and verified the underlying data reported in the manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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Data availability

The data used in this study were obtained from the National Health and Nutrition Examination Surveys (NHANES), which are publicly available from the Centers for Disease Control and Prevention (CDC) at https://www.cdc.go

v/nchs/nhanes/index.htm. Researchers interested in accessing the same data can obtain it directly from the NHANES database.

Declarations

Ethics approval and consent to participate

This study utilized publicly available data from the National Health and Nutrition Examination Survey (NHANES). The NHANES protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided informed consent. The study strictly adhered to the principles outlined in the Declaration of Helsinki. As this study involved secondary analysis of de-identified data, additional ethical approval was not required.

Institutional review board statement

National Health and Nutrition Examination Surveys (NHANES) is managed by the National Center for Health Statistics (NCHS), and its research protocol has received approval from the NCHS Institutional Review Board. Written informed consent is obtained from all participants.

Competing interests

The authors declare no competing interests.

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References

1. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart disease and stroke statistics-2023 update: A report from the American heart association. Circulation. 2023;147:e93–621.
2. Centers for disease control and prevention. National center for health statistics mortality data on cdc wonder. https://wonder.cdc.gov/mcd.html
3. U.S. Department of health and human services agency for toxic substancesand disease registry. Toxguide[tm] Cobalt. https://www.atsdr.cdc.gov/toxguides/toxguide-33.pdf
4. Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. Espen micronutrient guideline. Clin Nutr. 2022;41:1357–424.
5. Shakeri MT, Nezami H, Nakhaee S, Aaseth J, Mehrpour O. Assessing heavy metal burden among cigarette smokers and non-smoking individuals in Iran: cluster analysis and principal component analysis. Biol Trace Elem Res. 2021;199:4036–44.
6. Offringa AK, Bourgonje AR, Schrier MS, Deth RC, van Goor H. Clinical implications of vitamin b12 as redox-active cofactor. Trends Mol Med. 2021;27:931–4.
7. Leyssens L, Vinck B, Van Der Straeten C, Wuyts F, Maes L. Cobalt toxicity in humans-a review of the potential sources and systemic health effects. Toxicology. 2017;387:43–56.
8. Jenkinson MRJ, Meek RMD, Tate R, MacMillan S, Grant MH, Currie S. Cobalt-induced cardiomyopathy - do Circulating Cobalt levels matter? Bone Joint Res. 2021;10:340–7.
9. Tvermoes BE, Paustenbach DJ, Kerger BD, Finley BL, Unice KM. Review of Cobalt toxicokinetics following oral dosing: implications for health risk assessments and metal-on-metal hip implant patients. Crit Rev Toxicol. 2015;45:367–87.
10. Xu J, White AJ, Niehoff NM, O'Brien KM, Sandler DP. Airborne metals exposure and risk of hypertension in the sister study. Environ Res. 2020;191:110144.
11. Wu W, Jiang S, Zhao Q, Zhang K, Wei X, Zhou T, et al. Associations of environmental exposure to metals with the risk of hypertension in China. Sci Total Environ. 2018;622–623:184–91.
12. Yim G, Wang Y, Howe CG, Romano ME. Exposure to metal mixtures in association with cardiovascular risk factors and outcomes: A scoping review. Toxics. 2022;10.
13. Zhu Q, Liao S, Lu X, Shi S, Gong D, Cheang I, et al. Cobalt exposure in relation to cardiovascular disease in the united States general population. Environ Sci Pollut Res Int. 2021;28:41834–42.
14. Packer M. Cobalt cardiomyopathy: A critical reappraisal in light of a recent resurgence. Circ Heart Fail. 2016;9.
15. Sahoo K, Sharma A. Understanding the mechanistic roles of environmental heavy metal stressors in regulating ferroptosis: adding new paradigms to the links with diseases. Apoptosis: Int J Program Cell Death. 2023;28:277–92.
16. Liu Y, Zhu W, Ni D, Zhou Z, Gu JH, Zhang W, et al. Alpha lipoic acid antagonizes cytotoxicity of Cobalt nanoparticles by inhibiting ferroptosis-like cell death. J Nanobiotechnol. 2020;18:141.
17. Figgitt M, Newson R, Leslie IJ, Fisher J, Ingham E, Case CP. The genotoxicity of physiological concentrations of chromium (cr(iii) and cr(vi)) and Cobalt (co(ii)): an in vitro study. Mutat Res. 2010;688:53–61.
18. Fan Y, Tao C, Li Z, Huang Y, Yan W, Zhao S, et al. Association of endocrine-disrupting chemicals with all-cause and cause-specific mortality in the U.S.: A prospective cohort study. Environ Sci Technol. 2023;57:2877–86.
19. Duan W, Xu C, Liu Q, Xu J, Weng Z, Zhang X, et al. Levels of a mixture of heavy metals in blood and urine and all-cause, cardiovascular disease and cancer mortality: A population-based cohort study. Environ Pollution (Barking Essex: 1987). 2020;263:114630.
20. Zhao S, Wang S, Yang X, Shen L. Dose-response relationship between multiple trace elements and risk of all-cause mortality: A prospective cohort study. Front Nutr. 2023;10:1205537.
21. Princivalle A, Iavicoli I, Cerpelloni M, Franceschi A, Manno M, Perbellini L. Biological monitoring of Cobalt in hard metal factory workers. Int Arch Occup Environ Health. 2017;90:243–54.
22. Centers for disease control and prevention. National center for health statistics. National health and nutrition examination survey. https://www.cdc.gov/nchs/nhanes/index.htm
23. Centers for disease control and prevention. National center for health statistics. Nchs data linkage. 2019 public-use linked mortality files. https://www.cdc.gov/nchs/data-linkage/mortality-public.htm
24. Centers for disease control and prevention. National center for heath statistics. National health and nutrition examination survey. Weighting. https://www.cdc.gov/nchs/nhanes/tutorials/Weighting.aspx
25. Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the U.S. Population: implications for urinary biologic monitoring measurements. Environ Health Perspect. 2005;113:192–200.
26. Tellez-Plaza M, Navas-Acien A, Menke A, Crainiceanu CM, Pastor-Barriuso R, Guallar E. Cadmium exposure and all-cause and cardiovascular mortality in the U.S. General population. Environ Health Perspect. 2012;120:1017–22.
27. Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. Low-level lead exposure and mortality in Us adults: A population-based cohort study. Lancet Public Health. 2018;3:e177–84.
28. Daly LE. Confidence limits made easy: interval Estimation using a substitution method. Am J Epidemiol. 1998;147:783–90.
29. Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. Nat Rev Cardiol. 2015;12:627–42.
30. Tunstall-Pedoe H, Woodward M, Brown CA. The drinking, passive smoking, smoking deception and serum cotinine in the Scottish heart health study. J Clin Epidemiol. 1991;44:1411–4.

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