Increased Serum Levels of Cadmium are Associated with an Elevated Risk of Cardiovascular Disease in Adults

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Abstract

Previous studies have determined the effects of exposure to some heavy metals on cardiovascular disease (CVD); however, the association between exposure to cadmium and CVD in adults remains unclear. The relationship between serum levels of cadmium and the risk of CVD was studied by analysing available data from 38,223 participants who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2016. After adjusting for all covariates, we found that higher serum cadmium concentrations were positively related to both the overall risk of CVD (odds ratio (OR): 1.45; 95% confidence interval (CI): 1.22, 1.72; p for trend <0.001) and the risks of its subtypes, including congestive heart failure, coronary heart disease, heart attack and stroke. Elevated levels of cadmium were associated with increased levels of lipids and inflammation parameters, including blood triglycerides, total cholesterol, white blood cells (WBCs) and C-reactive protein (CRP). Our study provided epidemiological evidence that cadmium may increase the risk of CVD by elevating blood lipids and inflammation.

Capsule

High blood levels of Cd are associated with increased risks of overall CVD and four of the CVD subtypes

1. Introduction

Cardiovascular diseases (CVDs), which include heart and vasculature diseases such as coronary heart disease (CHD), angina, heart attack (HA), heart failure (HF) and stroke, is a leading cause of death worldwide.(Xu et al. 2020a) According to a report from the American Heart Association (AHA) in 2010, CVD mortality accounted for nearly 33% of all mortality; and one person died from CVD every 38 seconds. Moreover, more than 785,000 people were estimated to have new or recurrent CVD every year.(Lloyd-Jones et al. 2010) Therefore, determining and controlling the risk factors for CVD are critical.(Phillips &Guazzi 2015, Thiara 2015) Some new risk factors were recently identified in addition to traditional factors, such as smoking, high cholesterol, physical inactivity, obesity and diabetes.(Aw et al. 2020, Koller &Agyemang 2020, Lloyd-Jones et al. 2010, Zhang et al. 2020). In particular, environmental pollution was found to contribute to the development of CVD and its risk factors.(Bi et al. 2020, Li et al. 2020c, So et al. 2020, Xu et al. 2020a) Of these, heavy metal pollutants (methylmercury, lead, chromium, etc.), which constitute one type of environmental pollutant, are associated with CVD and its risk factors.(Ali et al. 2020, Cao et al. 2020, Orisakwe et al. 2020) However, few studies have addressed the correlation between cadmium and CVD.

Cadmium (Cd) is a toxic heavy metal that is found in soil, water, seafood and vegetables.(Dennis et al. 2020, Gameda et al. 2020, Koker et al. 2020, Orisakwe et al. 2015, Zhao et al. 2016) Many regions have reported levels of Cd exceeding the maximum permissible limit of 0.3 mg.kg^{-1} established by the World Health Organization (WHO).(Li et al. 2020a, Orisakwe et al. 2015, Orisakwe et al. 2020, Pan et al. 2016, Wang et al. 2018) In addition to natural sources, various human activities can increase levels of Cd,

including smoking, traffic emissions, metallurgical processes, nuclear energy production, mining, coal combustion and chemical manufacturing.(Li et al. 2019, Li et al. 2018, Sall et al. 2020, Wu et al. 2019) Furthermore, similar to other heavy metals, the stability and permeation of Cd lead to its persistence and accumulation in vivo.(Wang et al. 2015, Wu et al. 2019) Therefore, the relationships between Cd and many diseases have attracted considerable attention. Cd was found to increase not only the risk of carcinogenesis but also noncancer-related mortality;(Al Amin et al. 2020, Amadou et al. 2020, Suwazono et al. 2020) exposure to Cd was shown to be associated with kidney function decline, the development of neurodevelopmental disorders and inflammation of the airways.(Ijomone et al. 2020, Klein et al. 2020, Sotomayor et al. 2020) In addition, Cd was associated with elevated lipid levels and atherogenic indices, which might induce CVD in susceptible people.(Igharo et al. 2020, Xu et al. 2020b)

However, few studies have identified the relationship between Cd and CVD. A study in a Korean population showed that Cd was associated with the risk of stroke in people under the age of 60 years. An investigation in a larger and more representative population was needed to determine the correlation between the levels of Cd and CVD.(Jeong et al. 2020) Therefore, 38,223 subjects were included in this large population-based study based on data from the National Health and Nutrition Examination Survey (NHANES). Interestingly, the results showed that serum levels of Cd were positively related to CVD and its risk factors in adults.

2. Material And Methods

2.1 Subjects

We included subjects who had participated in the NHANES, which is a program of studies involving members of the general, non-institutionalized population in the United States. The detailed survey design, methods, and available data are accessible on the NHANES website.

(<https://www.cdc.gov/nchs/nhanes/>) The subjects who participated in the NHANES, had available serum heavy metal concentrations and had CVD from 1999 to 2016 were enrolled in our study. In total, 92,062 adults completed the interviews and examinations, and those who were pregnant or had missing data were excluded. Figure 1 shows the participant selection process. Finally, our study enrolled 38,223 participants.

2.2 Evaluation of outcomes

The participants were evaluated by both a standardized medical questionnaire and self-reported physician diagnoses. The participants reported whether doctors or other health professionals had ever diagnosed them with CHD, congestive HF, angina, stroke or HA. A participant was considered to have CVD if a positive response was given to any of the relevant questions. The blood concentrations of lipids were measured by Roche Modular P and Roche Cobas 6000 chemistry analysers and the Friedewald equation. The Beckman Coulter method was used to measure the parameters of inflammation.

2.3 Exposure to cadmium

Whole-blood samples were collected by a trained investigator and frozen before analysis. First, the blood samples were diluted. Then the serum cadmium levels were measured with an inductively coupled plasma mass spectrometer with dynamic reaction cell technology (ELAN® DRC II; PerkinElmer Norwalk, CT, USA). The quality assurance and quality control protocols followed the 1988 Clinical Laboratory Improvement Act mandates (<https://www.cdc.gov/nchs/nhanes/index.htm>).

2.4 Covariate

The covariates included age, sex, race, physical activity level, education level, poverty to income ratio (PIR), past-year alcohol consumption status, category of serum cotinine level, body mass index (BMI), family history of CVD and fish consumption; these covariates were selected based on factors that could affect the correlation between Cd levels and CVD risk. We treated age and PIR as continuous variables. Other variables were treated as categorical variables.

2.5 Statistical analysis

Continuous variables are presented as the means with standard deviations (SDs), and categorical variables are presented as frequencies and percentages. We compared continuous variables and categorical variables between groups with and without CVD with the Mann-Whitney U test and χ^2 tests, respectively, and analysed the correlations between the serum levels of heavy metals and the risk of CVD by survey-weighted multiple logistic regression analysis with three separate models. Model 1 was a crude model; Model 2 was adjusted for age, sex, race and education level; and Model 3 was adjusted for the variables included in Model 2 and BMI, PIR, physical activity, past-year alcohol consumption, serum cotinine, history of CVD, and fish consumption. We further investigated the relationships between serum concentrations of heavy metals and five CVD subtypes. Finally, multivariate analysis was used to explore the associations between serum Cd levels and blood lipids and inflammation parameters. Sampling weights were adjusted in all statistical analyses in SAS (version 9.2) and R software (version 3.5.0). We considered $P < 0.05$ to indicate statistical significance in this study.

3. Results

The demographics of the participants are shown in Table 1. Significant differences were found between subjects with and without CVD for age, sex, race, education level, PIR, physical activity level, past-year alcohol consumption, family history of CVD, serum cotinine category, BMI category and fish consumption.

Table 1
Participants characteristics (N = 38,223) in NHANES 1999–2016.

	Non-CVD	CVD	P value
Age (years)	45.30 ± 0.20	64.60 ± 0.30	< 0.001
Gender (%)			< 0.001
Male	48.40	53.20	
Race (%)			< 0.001
Mexican American	8.12	4.08	
Other Hispanic	5.63	3.22	
Non-Hispanic White	69.39	76.74	
Non-Hispanic Black	10.65	10.96	
Other Race - Including Multi-Racial	6.21	4.99	
Education Level (%)			< 0.001
Less Than 9th Grade	5.97	12.16	
9-11th Grade	11.56	16.86	
High School Grad/GED or Equivalent	23.73	26.98	
Some College or AA degree	30.79	26.37	
College Graduate or above	27.85	17.49	
Missing	1.05	1.34	
Family PIR (%)			0.001
< 1	12.80	15.94	
>=1	80.49	77.01	
Missing	6.71	7.05	
Physical activity (%)			< 0.001
Never	44.77	54.23	
Moderate	26.01	26.29	
Vigorous	28.47	14.34	

Mean ± SD. Percentage.

NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; CVD, cardiovascular disease; PIR, poverty to income ratio; LOD, limit of detection.

	Non-CVD	CVD	P value
Missing	0.76	5.15	
Past-year alcohol drinking (%)			< 0.001
No	22.25	30.08	
Yes	70.43	63.45	
Missing	7.32	6.47	
Family history of CVD (%)			< 0.001
No	77.52	66.34	
Yes	20.36	30.24	
Missing	2.12	3.42	
Serum cotinine category (%)			< 0.001
<LOD	20.66	20.49	
LOD-10	51.46	51.48	
> 10	26.60	25.98	
Missing	1.28	2.05	
BMI category (%)			< 0.001
< 25	32.70	21.68	
25–30	33.53	32.59	
>=30	32.57	41.93	
Missing	1.19	3.81	
Fish consumption			< 0.001
No	14.05	13.08	
Yes	66.00	60.22	
Missing	19.96	26.70	
Mean ± SD. Percentage.			
NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; CVD, cardiovascular disease; PIR, poverty to income ratio; LOD, limit of detection.			

Table 2 shows the correlations between the quartiles of the serum concentrations of three heavy metals and the risk of overall CVD according to the multivariate logistic regression model after adjustment for covariates. After adjusting for all covariates (model 3), we found that the risk of overall CVD was 1.45

times (95% CI: 1.22, 1.72; p for trend < 0.001) higher in the group with the highest quartile of serum Cd concentrations than in the group with the lowest quartile of serum Cd concentrations. No significant association was found between the other heavy metals and the risk of CVD.

Table 2
Multivariable correlations of selected heavy metals with cardiovascular disease (CVD) risk.

	Q1	Q2	Q3	Q4	P for trend
Lead					
Model 1	Ref	1.79 (1.54, 2.08)	2.91 (2.51, 3.36)	4.00 (3.46, 4.63)	< 0.001
Model 2	Ref	0.93 (0.79, 1.08)	1.10 (0.94, 1.29)	1.09 (0.94, 1.27)	0.025
Model 3	Ref	0.91 (0.76, 1.08)	1.05 (0.88, 1.25)	0.98 (0.82, 1.18)	0.432
Cadmium					
Model 1	Ref	1.66 (1.47, 1.86)	2.53 (2.24, 2.86)	2.73 (2.38, 3.12)	< 0.001
Model 2	Ref	0.99 (0.88, 1.13)	1.18 (1.03, 1.36)	1.58 (1.37, 1.82)	< 0.001
Model 3	Ref	0.97 (0.83, 1.12)	1.21 (1.04, 1.42)	1.45 (1.22, 1.72)	< 0.001
Mercury					
Model 1	Ref	0.92 (0.81, 1.05)	0.80 (0.70, 0.90)	0.76 (0.65, 0.89)	0.003
Model 2	Ref	0.88 (0.76, 1.02)	0.73 (0.63, 0.83)	0.70 (0.59, 0.82)	0.002
Model 3	Ref	0.94 (0.81, 1.08)	0.81 (0.70, 0.93)	0.82 (0.69, 0.96)	0.059
model 1: crude model;					
model 2: adjust for age, sex, race, education;					
model 3: model 2 plus, BMI, PIR, physical activity, past-year alcohol drinking, serum cotinine, family history of CVD, fish consumption and cycle.					

We further analysed the correlations between the risk of the five common subtypes of CVD (congestive heart failure, coronary heart disease, angina, heart attack and stroke) and the quartiles of the serum concentrations of the three heavy metals (Table 3). After adjusting for all covariates, the serum levels of Cd were positively related to the risk of congestive heart disease (OR = 1.53, 95% CI: 1.17, 2.00, p for trend < 0.001), CHD (OR = 1.24, 95% CI: 0.98, 1.55, p for trend = 0.005), HA (OR = 1.61, 95% CI: 1.28, 2.02, p for trend < 0.001) and stroke (OR = 1.68, 95% CI: 1.26, 2.23, p for trend < 0.001).

Table 3

Multivariable correlations of selected heavy metals with individual cardiovascular disease (CVD) risk.

	Congestive heart failure	Coronary heart disease	Angina	Heart attack	Stroke
Lead					
Q1	Ref	Ref	Ref	Ref	Ref
Q2	1.09 (0.84, 1.41)	0.98 (0.77, 1.25)	0.86 (0.65, 1.14)	1.22 (0.95, 1.58)	0.98 (0.78, 1.23)
Q3	0.97 (0.72, 1.30)	0.99 (0.78, 1.27)	0.87 (0.66, 1.15)	1.22 (0.94, 1.57)	1.16 (0.90, 1.49)
Q4	1.06 (0.81, 1.38)	0.99 (0.76, 1.29)	0.85 (0.62, 1.17)	1.26 (0.99, 1.60)	1.17 (0.89, 1.54)
P for trend	0.781	0.565	0.005	0.152	0.086
Cadmium					
Q1	Ref	Ref	Ref	Ref	Ref
Q2	0.98 (0.77, 1.24)	0.90 (0.72, 1.13)	1.03 (0.82, 1.30)	0.90 (0.71, 1.15)	1.20 (0.90, 1.58)
Q3	1.35 (1.06, 1.72)	1.19 (0.95, 1.47)	1.11 (0.90, 1.38)	1.36 (1.09, 1.71)	1.32 (1.00, 1.73)
Q4	1.53 (1.17, 2.00)	1.24 (0.98, 1.55)	1.07 (0.81, 1.40)	1.61 (1.28, 2.02)	1.68 (1.26, 2.23)
P for trend	< 0.001	0.005	0.161	< 0.001	< 0.001
Mercury					
Q1	Ref	Ref	Ref	Ref	Ref
Q2	0.89 (0.72, 1.09)	0.95 (0.75, 1.18)	0.99 (0.78, 1.26)	0.99 (0.81, 1.21)	0.86 (0.70, 1.06)
Q3	0.66 (0.50, 0.86)	0.95 (0.74, 1.23)	0.92 (0.71, 1.19)	0.83 (0.66, 1.04)	0.81 (0.67, 0.99)
Q4	0.55 (0.44, 0.68)	1.18 (0.90, 1.54)	0.92 (0.70, 1.20)	1.03 (0.83, 1.27)	0.61 (0.47, 0.80)
P for trend	0.041	0.019	0.419	0.634	0.003
Adjust for age, gender, race, education, BMI, PIR, physical activity, past-year alcohol drinking, serum cotinine, family history of CVD, fish consumption and cycle.					

Table 4 shows the relationships between levels of Cd and concentrations of blood lipids and inflammation parameters. After adjusting for all covariates, cadmium levels were positively related to the levels of serum triglycerides (Beta = 7.85, 95% CI: 2.78, 12.93, p = 0.003), total cholesterol (Beta = 0.03, 95% CI: 0.01,0.06, p = 0.021), and C-reactive protein (CRP, Beta = 0.03, 95% CI: 0.01,0.05, p = 0.009) and the WBC count (Beta = 0.26, 95% CI: 0.20,0.32, p < 0.001).

Table 4

Multivariate analysis of the association of the serum cadmium levels and concentration changes (95% CI) in the blood lipids and inflammation parameters.

	Beta	95% CI	P value
Serum triglyceride (mg/dL)	7.85	2.78, 12.93	0.003
HDL-cholesterol (mg/dL)	0.18	-0.32, 0.67	0.471
LDL-cholesterol (mg/dL)	0.54	-0.83, 1.91	0.438
Total cholesterol (mg/dL)	0.03	0.01, 0.06	0.021
WBC (10 ⁹ /mL)	0.26	0.20, 0.32	< 0.001
CRP (mg/dL)	0.03	0.01, 0.05	0.009
Adjust for age, sex, race, education, BMI, PIR, physical activity, past-year alcohol drinking, serum cotinine, family history of CVD, fish consumption, lead, mercury and cycle.			
CI, confidence interval; HDL, high density lipid; LDL, low density lipid; WBC, white blood cell; CRP, C-reactive protein.			

4. Discussion

Our large population-based study is the first to show a dose-response relationship between cadmium (Cd) and cardiovascular disease (CVD) in adults. Furthermore, the serum levels of Cd were positively related to the overall risk of CVD and the risks of four of the subtypes. The underlying mechanism may involve the increases in blood lipid levels and activation of the inflammatory response induced by Cd.

Few previous studies have focused on the relationship between the levels of Cd and CVD in adults. Although a study involving 15,624 United States (US) adults showed that urinary levels of Cd might be associated with all-cause mortality, more than 30% of which was attributed to CVD, no significant association was observed between Cd levels and CVD mortality.(Kim et al. 2019) Given that the levels of urinary Cd are sensitive to kidney function and physical activity, they cannot be used to accurately reflect exposure levels.(Li et al. 2020b, Munoz et al. 2020) The association of blood levels of Cd with CVD was studied in another population, and it was shown that elevated levels of Cd were associated with an elevated risk of CVD in adults under 60 years old.(Jeong et al. 2020) Nevertheless, given that the investigated population consisted of a single ethnicity, had fewer subtypes of CVD and was not adjusted for the confounding effects of smoking,(Li et al. 2019) this finding lacks generalizability. Therefore, our

study provided valid evidence of the relationship between Cd levels and CVD risk after overcoming the abovementioned limitations. Further analysis is needed to investigate the underlying mechanisms by which Cd affects CVD; these mechanisms may involve the relationships between Cd and the levels of triglycerides, total cholesterol, and CRP and the WBC count.

Our results showed that the levels of Cd were positively correlated with the blood levels of triglycerides and total cholesterol, which indicated that elevated levels of triglyceride and total cholesterol may play important mediating roles in Cd-related CVD. Consistent with our findings, there is a substantial amount of evidence that exposure to Cd can result in dyslipidaemia, which has been identified as a risk factor for CVD.(Samarghandian et al. 2015, Zhu et al. 2020) Indications of the possible underlying mechanisms can be found in the results of this study and previous studies. An animal study showed that Cd could increase triglyceride levels by reducing lipid uptake receptors in the liver.(Liu et al. 2020a) In addition, exposure to Cd also initiated the endoplasmic reticulum (ER) stress process, which negatively affected lipid homeostasis and metabolic gene expression.(Rajakumar et al. 2020) Furthermore, high levels of Cd could also increase the production of lipids by markedly elevating the activity of serum lipase, reduce lipid degradation by reducing fatty acid β oxidation and promote lipid synthesis by modifying many liver enzymes, such as hydroxyl-methyl-glutaryl CoA reductase (HMG-CoA).(Aja et al. 2020, Ali et al. 2020, Pawlak et al. 2015, Wu et al. 2017)

Our study also suggested that WBC counts and CRP levels were positively associated with Cd levels, which provides insight into another possible mechanism underlying Cd-related CVD. Although many studies have reported high levels of WBCs in patients with CVD, the reason is unclear.(Koren-Morag et al. 2005, Lassale et al. 2018, Xu et al. 2020a) Interestingly, some studies showed that changes in WBC counts and CRP levels indicated systemic inflammation.(Baek & Chung 2017, Fagerberg et al. 2017, Saggu et al. 2019) It is worth noting that reactive oxygen species (ROS), autophagy, and immune-related and apoptosis-related genes were found to be involved in this process, which possibly increased the risk of CVD by inducing cytotoxicity, vascular toxicity, nephrotoxicity and cardiotoxicity.(Kwok & Chan 2020, Kwok et al. 2020, Liu et al. 2020b, Reyes-Becerril et al. 2019, Roy et al. 2020, Wang et al. 2020)

Our study had some limitations. First, due to its long biological half-life and low excretion rate, it was difficult to determine whether the timing of exposure to Cd influenced the CVD risk in our study.(Bhardwaj et al. 2020, Kabamba & Tuakuila 2020) In addition, genetic factors also contribute to the risk of CVD; however, there were no genetic data collected in the NHANES. Although the results also showed that levels of mercury were positively related to the risks of congestive HF and stroke, our study mainly addressed the relationship between Cd levels and the risk of CVD. Finally, as this was a cross-sectional study, it can only provide epidemiological evidence of a correlation between Cd levels and the risk of CVD, and further functional experiments and prospective cohort studies are needed to verify this correlation.

5. Conclusion

In our study, high serum levels of Cd are associated with increased risks of overall CVD and four of the CVD subtypes and that the concentrations of Cd are also positively related to the levels of lipids and inflammation parameters, which might provide insight into the possible mechanism underlying Cd-related CVD.

Declarations

Availability of data and material

Data will be available on request.

Authors' contributions

Xuming Mo: Conceptualization, Validation, Supervision and Funding acquisition. Siyu Ma: Methodology, Writing - Original Draft and Visualization. Cheng Xu: Methodology, Formal analysis and Visualization. Jie Zhang: Supervision and Project administration. Min Da, Yang Xu and Yong Chen: Resources.

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Conflicts of interests

The authors declare that they have no competing interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

Not applicable

Consent for publication

Not applicable

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Figures

Figure 1

Participant selection process for the analyses of the relationships between serum cadmium levels and the risk of cardiovascular disease (CVD) in adults.

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