
Brief communication

Association between blood cadmium levels and the risk of chronic kidney disease in Korea, based on the Korea National Health and Nutrition Examination Survey 2016–2017

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Abstract

Background: Exposure to environmental cadmium can have harmful effects on the human kidneys. The relationship between the degree of exposure to cadmium and the risk of chronic kidney disease (CKD) in the general population is unclear.

Objectives: To investigate the association between blood cadmium levels and CKD risk using samples from the Korea National Health and Nutrition Examination Survey (KNHANES) VII data, which included heavy metal and serum creatinine levels.

Methods: We analyzed the data of 4,222 adults from January 1, 2016, to December 31, 2017. Multiple logistic regression analysis was conducted on weighted data using complex sampling to assess the relationship between blood cadmium levels and CKD. We performed a stratified analysis in the presence of comorbidities such as diabetes or hypertension.

Results: There was a positive association between blood cadmium level and the risk of CKD in hypertensive or nondiabetic participants after adjustment, but not between blood cadmium level and CKD in normotensive or diabetic participants. The corresponding odds ratios (OR) of cadmium for CKD were 2.70 (95% confidence interval [CI], 1.49–4.90, $P = 0.001$) in samples with hypertension and 2.40 (95% CI, 1.56–3.70, $P < 0.001$) in samples without diabetes.

Conclusions: Our findings suggest an association between blood cadmium level and the risk of CKD in hypertensive or nondiabetic participants. Additional research is necessary to elucidate the relationship between cadmium exposure and CKD risk, particularly in individuals with comorbidities.

Keywords: cadmium; chronic kidney disease; diabetes; hypertension; KNHANES

Chronic kidney disease (CKD), characterized by renal dysfunction, is a growing public health problem with a profound impact on individuals and society as a whole [1]. CKD is currently one of the most important causes of death and morbidity [2]. As risk factors such as diabetes and hypertension gradually increase, the prevalence of CKD continues to

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increase, and as of 2017, >10% of the world's population, that is, 800 million people, are suffering from CKD [2, 3]. Cadmium is one of the environmental heavy metals and is present in the air, soil, seafood, cigarettes, and children's plastic toys [4]. Therefore, humans are commonly exposed to cadmium which gradually accumulates in the body. The kidneys are the main organs affected by environmental cadmium exposure during everyday life and are also vulnerable to cadmium toxicity [5]. However, the association between exposure to cadmium and CKD in the population nationwide is not yet clear.

While acute cadmium toxicity is now rare in most countries, chronic cadmium toxicity is mainly characterized by dysfunction of the kidney's proximal tubule, leading to a decreased glomerular filtration rate (GFR). Although the general effect of cadmium on proximal tubule function is known in respect of large quantities through previous studies, the basic mechanism for this effect is not adequately revealed [6]. Oxidative stress has been reported to cause renal tissue damage and is an important contributor to chronic inflammation leading to further tissue injury [7, 8]. Some researchers have shown that cellular death could also be mediated by lipid peroxidation induced by cadmium [9, 10].

The objective of the present study was to evaluate the hypothesis that people with high blood cadmium levels are at a greater risk of developing CKD compared with people with low blood cadmium levels. We examined this in the Korea National Health and Nutrition Examination Survey (KNHANES) VII (2016–2017). Kidney damage was evaluated by measuring an estimated glomerular filtration rate (eGFR). To control for other risk factors of CKD, we performed a stratified analysis in the context of comorbidities, including diabetes and hypertension.

Methods

Study population

The present study utilized samples from the KNHANES VII (2016–2017) survey data, which included heavy metal and serum creatinine levels. The KNHANES is a nationally representative, population-based, cross-sectional survey conducted each year by the Korea Centers for Disease Control and Prevention (KCDC) [11]. It assessed the health and nutritional status of Koreans, which consisted of 3 components: health interview, health examination, and nutrition. The KNHANES data are publicly available and can be obtained from the KNHANES website (<https://knhanes.kdca.go.kr>). In the 2016–2017 KNHANES, 16,277 participants were selected by using two-stage stratified cluster sampling. In this study, all populations from the 2016 and 2017 KNHANES with measured blood cadmium levels and serum creatinine concentrations were included. We excluded those under 30 years of age and those with incomplete information such as missing data on body mass index (BMI), hypertension, diabetes mellitus, and dyslipidemia from our analysis (**Figure 1**).

Blood cadmium levels

The blood cadmium levels were measured partly by randomly subsampling in the KNHANES in 2016 and 2017. The concentration of blood cadmium was assessed by graphite furnace atomic absorption spectrophotometry (GFAAS) using AAnalyst600 (PerkinElmer, Turku, Finland) and presented as microgram per liter.

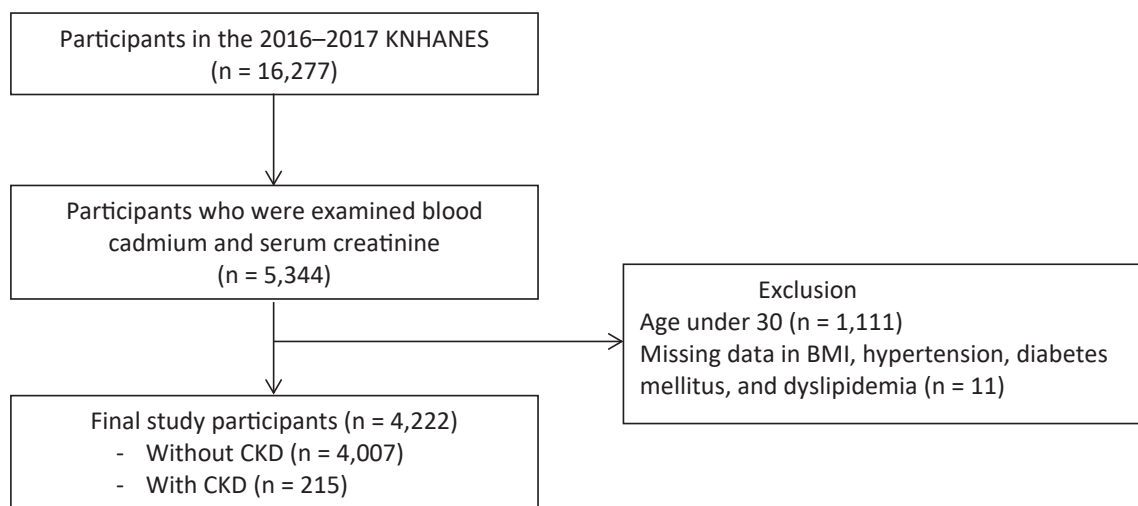


Figure 1. Schematic diagram of participant selection. BMI, body mass index; CKD, chronic kidney disease.

CKD

In the current study, CKD was defined as the eGFR <60 mL/min/1.73m² according to the Kidney Disease Improvement Global Outcome (KDIGO) 2012 guidelines [12]. The eGFR was calculated using the following formula according to the Modification of Diet in Renal Disease (MDRD):

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female).}$$

Unfortunately, in the KNHANES VII (2016–2017), the urine albumin-to-creatinine ratio (ACR) value was not available because the urine albumin was not measured.

Confounders

Covariate variables to minimize confounding bias included age, sex, BMI, and physician-diagnosed hypertension, diabetes mellitus, or dyslipidemia. Age was categorized into 3 groups: 30–50 years, 50–70 years, and >70 years. Hypertension, diabetes, and dyslipidemia were evaluated by the question, “Have you ever been diagnosed with hypertension, diabetes, or dyslipidemia by a physician?”

Ethical statement

This study protocol was approved by the Institutional Review Board of the Kangbuk Samsung Hospital (2022-07-051). All participants provided written informed consent to the Korea Center for Disease Control and Prevention.

Statistical analysis

General participant characteristics according to CKD were compared with the Student’s *t* test for continuous variables and the chi-squared test for categorical variables. As the KNHANES follows a multistage clustered probability design, the sampling weights for each participant were constructed for unbiasedly representing the Korean population. The weights are adjustment factors assigned to each individual that account for the complex survey design as well as survey nonresponse and post-stratification. Multiple logistic regression analysis was performed on weighted data using complex sampling to evaluate the association between blood cadmium level and CKD. Multivariable model 1 was adjusted for age and sex, and multivariable model 2 was fully adjusted for age, sex, hypertension, diabetes mellitus, and dyslipidemia.

The statistical analyses were conducted using SPSS version 24.0 for Windows (IBM, Armonk, NY, USA).

Results

We used the data of 4,222 adults who participated in the KNHANES VII from January 1, 2016, to December 31, 2017. The baseline characteristics of the participants are shown in **Table 1**. Among the participants, the prevalence of CKD, hypertension, diabetes mellitus, and dyslipidemia was 215 (5.1%), 1,052 (24.9%), 461 (10.9%), and 831 (19.7%), respectively. The mean concentration of blood cadmium was 1.2 µg/L among all participants, with a higher mean blood cadmium in the CKD group than that in the non-CKD group (1.3 µg/L vs 1.1 µg/L, *P* < 0.001). The CKD group was significantly older, had a higher BMI, a higher proportion of men, and a higher prevalence of hypertension, diabetes mellitus, and dyslipidemia than the non-CKD group.

In the univariable logistic analysis, we found that the higher concentration of blood cadmium correlated significantly with the prevalence of CKD. After multivariable logistic regression analysis adjusted for age, sex, as well as full adjustment for confounding variables, including hypertension, diabetes mellitus, and dyslipidemia, blood cadmium level had a significant association with CKD, as shown in **Table 2**.

Additionally, we performed hypertension- and diabetes-stratified analyses of the association between blood cadmium and CKD (**Tables 3 and 4**). There was a positive association between blood cadmium and CKD in hypertensive or nondiabetic participants. However, there was no significant association between blood cadmium and CKD in normotensive or diabetic participants.

Discussion

From the results of analyzing 4,222 adults of KHNANES, there was a significant association between the risk of CKD and age, male sex, BMI, hypertension, diabetes, dyslipidemia, and blood cadmium level. Overall, this reflects consistent results regarding the risk factors of CKD reported in previous studies. However, the blood cadmium levels of all samples in our research were higher than those of previous studies [13, 14]. For instance, in data from the Korean National Human Exposure and Bio-monitoring Examination in 2010, the mean plasma cadmium concentration measured in 2,369 participants was 0.92 µg/L compared with 1.2 µg/L in our

Table 1. Characteristics of the 4,222 adults in the KNHANES

Parameters	All(n = 4,222)	CKD (n = 215)	CKD5	Non-CKD (n = 4,007)	P
Age (years)	54 ± 14	69 ± 10	53 ± 14	53 ± 14	<0.001†
30–49	1,737 (41.1%)	85 (39.5%)	1 (%)	1,652 (41.2%)	
50–69	1,773 (42.0%)	9 (4.2%)	3 (%)	1,764 (44.0%)	<0.001†
>70	712 (16.9%)	121 (56.3%)	1 (%)	591 (14.7%)	
Sex					
Male (%)	1,869 (44.3%)	112 (52.1)	5 (100)	1,757 (43.8%)	0.021*
BMI (kg/m ²)	24.1 ± 3.5	25.0 ± 3.8	26.0 ± 1.9	24.1 ± 3.5	0.001*
Hypertension	1,052 (24.9%)	149 (69.3%)	5 (100%)	903 (22.5%)	<0.001†
Diabetes	461 (10.9%)	78 (36.3%)	3 (60.0%)	383 (9.6%)	<0.001†
Dyslipidemia	831 (19.7%)	71 (33.0%)	3 (60.0%)	760 (19.0%)	<0.001†
Smoking	1,700 (40.3%)	94 (43.7%)	4 (80.0%)	1606 (40.1%)	0.29
Blood Cd (µg/L)	1.2 ± 0.6	1.3 ± 0.6	1.4 ± 0.9	1.1 ± 0.6	<0.001†

Data show mean ± standard deviation.

**P* < 0.05.

†*P* < 0.001.

BMI, body mass index; Cd, cadmium; CKD, chronic kidney disease; CKD5, stage 5 of CKD indicating an eGFR of <15 mL/min or less; eGFR, estimate glomerular filtration rate.

Table 2. Multiple logistic regression analysis for CKD by blood Cd in the 4,222 adults in the KHNANES

Variables	OR (95% CI)	P
Univariable model		
Blood Cd	1.59 (1.30–1.94)	<0.001†
Multivariable model 1		
Blood Cd	1.34 (1.01–1.79)	0.047*
Multivariable model 2		
Blood Cd	2.40 (1.58–3.64)	<0.001†

Multivariable model 1 includes adjustment for age and sex.

Multivariable model 2 includes adjustment for variables in age, sex, BMI, smoking, dyslipidemia, hypertension, and diabetes.

**P* < 0.05.

†*P* < 0.001.

BMI, body mass index; Cd, cadmium; CI, confidence interval; CKD, chronic kidney disease.

study [15]. In another study using data from the Fourth Korea National Health and Nutrition Examination Survey from 2007 to 2008, the mean blood cadmium in a representative sample of 1,709 Korean participants was 1.02 µg/L [16]. It appears that Koreans are gradually becoming more exposed to cadmium. In Korea, smoking, consuming a lot of vegetables, automobile smoke, and fine dust are considered to be sources of cadmium exposure.

Cadmium, a common heavy metal present in the everyday environment, is well known to be introduced into the human body through occupational or environmental exposure, causing adverse health effects [17]. Smoking is known to be

a major source of non-occupational cadmium exposure, so the blood cadmium levels in smokers are approximately 3–5 times higher than those in non-smokers [18, 19]. Tobacco contains various metal impurities such as cadmium and lead, with cadmium in particular known to significantly contribute to its accumulation within the body [20]. The influence of smoking and alcohol consumption on blood lead and cadmium levels depends on complex factors ranging from direct exposure increase to absorption and excretion [21]. Severe impairment of renal functions was also a risk factor for high blood cadmium levels, since cadmium is mainly excreted by the kidneys [22]. In this study, 40.3% of CKD patients were smokers, while 43.7% of the non-CKD group were smokers, with no statistically significant difference observed between the two groups. However, given that smoking may have a synergistic effect when accompanied by other risk factors, including alcohol consumption and cardiovascular diseases, even a slight increase of blood cadmium levels should not be disregarded from a public health perspective.

To date, the relationship between the degree of exposure to cadmium and the risk of CKD in the general population is still unclear. In a previous study, Kim et al. [23] reported that cadmium concentration and CKD occurrence correlated in patients with diabetes but not in patients without diabetes. According to the authors, cadmium contributed to the development of CKD with a synergic effect on kidney damage by diabetes and hypertension. However, blood cadmium concentration was associated with a higher risk of CKD in healthy people without diabetes in this study, whereas in

Table 3. Multiple logistic regression analysis for CKD by blood Cd according to hypertension

Variables	Hypertensive (n = 1,052)		Non-hypertensive (n = 3,170)	
	OR (95% CI)	P	OR (95% CI)	P
Univariable model				
Blood Cd	1.39 (1.02–1.91)	0.040*	1.72 (1.39–2.14)	<0.001†
Multivariable model 1				
Blood Cd	1.51 (1.05–2.15)	0.024*	0.94 (0.55–1.62)	0.83
Multivariable model 2				
Blood Cd	2.70 (1.49–4.90)	0.001†	2.16 (1.10–4.22)	0.025*

Multivariable model 1 includes adjustment for age and sex. Multivariable model 2 includes adjustment for variables in age, sex, BMI, smoking, dyslipidemia, and diabetes.

* $P < 0.05$.

† $P < 0.01$.

BMI, body mass index; Cd, cadmium; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratios.

Table 4. Multiple logistic regression analysis for CKD by blood Cd according to diabetes

Variables	Diabetic (n = 461)		Nondiabetic (n = 3,761)	
	OR (95% CI)	P	OR (95% CI)	P
Univariable model				
Blood Cd	1.19 (0.72–1.96)	0.500	2.08 (1.69–2.57)	<0.001†
Multivariable model 1				
Blood Cd	1.17 (0.68–2.03)	0.569	1.54 (1.08–2.18)	0.016*
Multivariable model 2				
Blood Cd	2.32 (0.70–7.75)	0.738	2.40 (1.56–3.70)	<0.001†

Multivariable model 1 includes adjustment for age and sex. Multivariable model 2 includes adjustment for variables in age, sex, BMI, smoking, and dyslipidemia.

* $P < 0.05$.

† $P < 0.001$.

BMI, body mass index; Cd, cadmium; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratios.

patients with diabetes, blood cadmium concentration was not associated with the risk of CKD. Recently, Wang et al. [24] reported that plasma cadmium was negatively associated with CKD in diabetes, which is consistent with our findings. Byber et al. [25] also reported that there was no evidence that exposure to cadmium was related to the risk of progression to CKD. There is still a lack of research on the relationship between low-level environmental exposure to cadmium and the risk of CKD in patients with comorbidities such as diabetes or hypertension. In the future, studies are needed in consideration of Asian genetic characteristics, dietary habits, and lifestyle.

There are limitations to this study. First, since the KNHANES is cross-sectional data, the causality between blood cadmium level and the risk of CKD cannot be determined. Prospective studies are needed to analyze the cause and effect, because only the association at one point can be known. Second, the results of this study were interpreted considering

only age, sex, BMI, diabetes, hypertension, and dyslipidemia as the confounding factors. However, many other clinical factors actually should be considered as risk factors for CKD. Researchers have recognized that risk factors for CKD include an individual's genetic factors, race, exposure to heavy metals, excessive alcohol consumption, smoking, and the use of analgesic medications [26]. A history of acute kidney injury, cardiovascular disease, metabolic syndrome, hepatitis C virus, HIV infection, and malignancy are considered to be further risk factors [27]. There is, therefore, a limitation in that the results of this study were derived without fully adjusting for all confounding factors.

The strength of this study is that the effect of blood cadmium level on CKD was analyzed from well-organized, high-quality data called KNHANES. The KNHANES is a national surveillance system that has been evaluating the health and nutritional status of Koreans conducted by the KCDC [11]. KNHANES data are important resources for tracking variations in risk

factors and disease trends. The KNHANES is a well-organized survey with nationally representative samples of Korea. Even if our findings are not in part consistent with existing studies, they can be a precursor to studying the potential effects and the underlying mechanism of cadmium.

As a result, even exposure to low-dose environmental cadmium can damage the kidneys and increase the risk of CKD. According to stratified analysis, cadmium concentration was associated with CKD in nondiabetic and hypertensive patients but not in diabetic patients. There might be other reasons that are not clearly identified in diabetic patients, which need to be further investigated.

Author contributions. JGS and JP conceived the study. JHA and SK did the data acquisition. SHL and KHR did interpretation of data. EAC did the statistical analysis. JY drafted the manuscript. JGS supervised and contributed to finalizing the manuscript.

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Conflict of interest disclosure. The authors declare no conflicts of interest.

Data sharing statement. Original and statistical summaries of the data generated and analyzed for the present study are included in this published article. Further details of the data are available from the corresponding author on reasonable request.

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