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ORIGINAL ARTICLE

# Blood cadmium and moderate-to-severe glomerular dysfunction in Korean adults: analysis of KNHANES 2005–2008 data

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**Abstract**
*Purpose* The objective of this study was to evaluate the association between blood cadmium (Cd) and moderate-to-severe glomerular dysfunction in a Korean population using a representative sample.
*Methods* A cross-sectional study was used to evaluate the association between blood Cd and glomerular dysfunction. Based on the Korean National Health and Nutrition Examination Survey (2005–2008), individual blood Cd was measured in 2,992 adults, aged between 20 and 65.
*Results* After adjusting for survey years, age, sociodemographic factors, and health behaviors, the odds ratio for moderate-to-severe glomerular dysfunction (<60 mL/min per 1.73 $m^2$) was 1.97 (95% CI: 1.28–3.07) when comparing the highest with the lowest blood Cd quartile in Korean women. However, in Korean men, there was no association between blood Cd and moderate-to-severe glomerular dysfunction.
*Conclusions* These findings support the consideration of Cd as a risk factor for glomerular dysfunction in the female population. Furthermore, environmental heavy metal monitoring and an institutional strategy should be implemented to reduce Cd exposure in the general population.

**Keywords** Cadmium · Glomerular filtration rate · Kidney diseases · KNHANES

## Introduction

Cadmium (Cd) is found naturally in the environment and is spread widely by different kinds of human activity. Exposure to Cd from occupational and environmental sources is known to cause toxicity in humans (Jarup and Akesson 2009; Jarup et al. 1998). Major sources of Cd are the industrial production and consumption of Cd, byproducts from the production of other non-ferrous metals, and the disposal of wastes containing Cd (World Health Organization (WHO) 1992). Cd is used in the production of batteries, pesticides, insecticides and fertilizers, electroplating, industrial pigments, and special welding techniques using metal alloys (Nordberg et al. 2007). Cd can be released into the environment by these processes. In the general non-smoking population, food (shellfish, grains, and vegetables from Cd-contaminated soil) is the primary source of chronic environmental exposure to Cd (European Food Safety Authority 2009; Kim and Wolt 2011; Olsson et al. 2002). Tobacco is also a major source of Cd uptake in smokers (Satarug and Moore 2004; Lewis et al. 1972; Akesson et al. 2005; Olsson et al. 2002).

It is estimated that 10–50% of inhaled Cd and a low percentage of Cd from the gastrointestinal tract is absorbed (Berglund et al. 1994; World Health Organization

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(WHO) 1992; Friberg et al. 1986). High-dose, absorbed Cd binds to high-molecular weight proteins in the blood and is delivered to the liver, where it binds to cysteine-rich low-molecular weight proteins, especially metallothionein (MT) (Groten et al. 1992). However, long-term, low-dose ingested Cd is absorbed by mucosal cells and binds to MT in the mucosa (Sorensen et al. 1993; Groten et al. 1991, 1992; Ohta and Cherian 1991). The Cd-MT complex is redistributed to all organs, filtered in the glomerulus, and reabsorbed in renal tubuli (Groten et al. 1992).

Accumulated Cd in the renal cortex causes renal tubular dysfunction, with impaired re-absorption of low-to-high-molecular weight proteins. Increased excretion of albumin and microalbuminuria may reflect glomerular lesions. Such glomerular lesions eventually influence the glomerular filtration rate (GFR) (World Health Organization (WHO) 1992; Jarup et al. 1998).

It has been reported that both high-dose (occupational) and low-dose (environmental) exposure to Cd are likely to influence renal dysfunction (Kobayashi et al. 2008; Akesson et al. 2005; Suwazono et al. 2006). According to research on low-dose Cd exposure and renal effects in the US and Sweden, a low daily dose of Cd can give rise to renal tubular disease (Navas-Acien et al. 2009; Akesson et al. 2005), and the prevalence of chronic kidney disease is 1.32 times higher in the highest quartile than in the lowest blood Cd quartile in the general US population (Navas-Acien et al. 2009). These reports suggest that low-dose Cd from environmental exposure may lead to renal damage.

Recently, it has been estimated that the daily Cd intake in the Korean population is 14.5–21.2 µg/day (Moon et al. 1995; Kim and Wolt 2011). The United Nations Environment Programme (UNEP) reported that average dietary cadmium intake (µg/kg per day) is 0.54 in the general Japanese population, where the pattern of food consumption is similar to that in Korea (Kim and Wolt 2011; Watanabe et al. 2000), but was 0.12–0.13 in the Swedish and 0.13–0.15 in the US general population (United Nations Environment Programme 2010). This indicates that environmental Cd exposure may lead to nephrotoxicity at the level of estimated daily Cd intake in the Korean population.

Few studies have evaluated the association between environmental low-dose Cd exposure and glomerular dysfunction (Navas-Acien et al. 2009; Jin et al. 2002), although epidemiological research does support a contribution of environmental lead exposure to renal disease (Navas-Acien et al. 2009). Furthermore, to our knowledge, there are few reported studies on environmental Cd exposure and glomerular dysfunction in general Asian populations.

The aim of this study was to evaluate the association between blood Cd and moderate-to-severe glomerular dysfunction in the Korean population, aged between 20 and 65, who participated in the Korean National Health and Nutrition Examination Survey (KNHANES) (2005–2008).

## Materials and methods

### Data source and study subjects

We used the Health Interview Survey for the heavy metal data set, derived from the publicly available third and fourth Korean National Health and Nutrition Examination Survey (KNHANES III, IV). The KNHANES III and IV surveys were conducted by Korea Center for Disease Control and Prevention in 2005 and from 2007 to 2008, respectively. A stratified, multistage, clustered probability design was used to select representative samples of non-institutionalized Korean civilians for the KNHANES, which has been performed periodically to estimate the health and nutritional status of the population of Korea. Additional details regarding study design and methods are reported elsewhere (Korea Center for Disease Control and Prevention 2011).

In total, 7,597 (70.2% response rate) and 9,744 (77.8% response rate) men and women participated in the health examination surveys of KNHANES III and IV, respectively. From those 20-year-olds or older who underwent a health examination in the 200 primary sampling units, 10–12 individuals from the unit were randomly selected while maintaining a uniform distribution across gender and five age groups (20–29, 30–39, 40–49, 50–59, and 60 years or older) to yield a total of 2,000 in KNHANES III and 2,006 subjects in KNHANES IV for heavy metal examination (Kim and Lee 2011; Korea Center for Disease Control and Prevention 2011). Because of missing information, data for two participants were excluded, and thus, 4,004 subjects were included in the final study. Those aged 65 or older ($n = 278$) or diagnosed with hypertension, diabetes, or kidney disease ($n = 731$) were excluded, as were those who gave incomplete responses in the health examination ($n = 3$), leaving a total of 2,992 subjects. The survey data were made publicly available, and ethics approval was not needed.

### Blood heavy metal determinations

Blood Cd and lead (Pb) analyses were carried out by the Seoul Medical Science Institute (SMSI) in KNHANES III and NEODIN Medical Institute (NMI) in KNHANES IV. Both laboratories were certified by the Korean Ministry of Health and Welfare. Intensive quality control was followed, including confirmation that background Cd and Pb did not contaminate collection or storage materials. Cd and Pb in whole blood were measured by graphite furnace atomic absorption spectrometry with Zeeman background correction (SPectrAA-800, Varian Instruments, Australia, in KNHANES III, and AAnalyst AAS-600, Zeeman correction, Perkin Elmer, Singapore, in KNHANES IV). For internal quality assurance and control purposes, standard reference materials were used from whole blood metals standard reference materials (Bio-Rad, USA), which showed that the coefficients of variation were 14.5 and 10.0% for blood Cd, and 8.5 and 10.0% for blood Pb samples in KNHANES III and KNHANES IV, respectively. The German External Quality Assessment Scheme (G-EQUAS), operated by Friedrick Alexander University, has a standard protocol for measuring heavy metals at low concentrations; this was used for external quality assurance and control. The limits of detection for Cd and Pb in blood were 0.30 μg/L and 0.23 μg/dL in KNHANES III and 0.087 μg/L and 0.0223 μg/dL in KNHANES IV, respectively. In total, there were eight and five participants with levels below the detection limit for Cd and Pb, respectively, in KNHANES III, but no subject was below the detection limit for Cd in KNHANES IV. For these participants, a level equal to the limit of detection divided by the square root of 2 was imputed (Glass and Gray 2001). Cd and Pb levels were divided into quartiles by gender.

## Measures of glomerular dysfunction

Serum creatinine was measured using the Jaffe method with an ADIVIA650 (Siemens, USA) in KNHANES III, and a Hitachi Automatic Analyzer 7600 (Hitachi, Japan) in KNHANES IV. For external quality control, both centers were certified by The Korean Association of Quality Assurance for Clinical Laboratories. For internal quality control, serum creatinine concentrations were calibrated to standard creatinine, and external quality assessments were made by the quality control team of the Korea Center for Disease Control. Both quality controls were satisfactory. Estimated GFR (eGFR) was calculated using the Modification of Diet in Renal Disease Study (MDRD) formula: eGFR (mL/min per 1.73 $m^2$) = 194 × (standardized serum creatinine in mg/dL)$^{-1.094}$ × (age in years)$^{-0.287}$, multiplied by 0.739 for women. We used the ethnic coefficient of the Japanese for Koreans (Matsuo et al. 2009), because there is no official ethnic coefficient for Koreans. Moderate-to-severe glomerular dysfunction was defined as <60 mL/min per 1.73 $m^2$, according to the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines (KDOQI Working Group 2002).

## Other variables

Information on age, gender, education, total household income per month, occupation, smoking, and alcohol consumption was based on the health questionnaire survey. Hemoglobin in whole blood was measured using the cyanmet-hemoglobin method with an ADVIA 120 (Bayer, USA) in KNHANES III and the SLS hemoglobin method with an XE-2100D analyzer (Sysmex, Japan) in KNHANES IV. Anemia was defined as hemoglobin below 12 g/dL for non-pregnant women, 11 g/dL for pregnant women, and 13 g/dL for men. We followed the classification of health behaviors in KNHANES III and IV (Korea Center for Disease Control and Prevention 2011). For smoking, subjects were classified into three categories (current/former/non). For drinking, the monthly frequency of drinking was estimated (less than once per month/more than once per month). Total household income was categorized into quartiles from Q1 (lowest) to Q4 (highest). Education was classified into four categories: education for 6 years or less as elementary school, 7–9 years as middle school, 10–12 years as high school, and 13 years or more as college and university. Occupational classifications followed the major groups of the Korean Standard Classification of Occupations (KSCO). Subjects were classified as manual workers (included agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and elementary occupations) and others (non-manual workers (managers, professionals, technicians, clerks, and service/sales workers) and those who were not in the labor market (unemployed, retired, students, and housewives)).

## Statistical analysis

All statistical analyses were performed using SAS 9.1 to account for the stratified multistage clustered probability design and survey weights. The distributions of Cd and Pb in blood were skewed and log-transformed for estimating the geometric mean, 95% confidence intervals, and quartiles. The odds ratio for moderate-to-severe glomerular dysfunction (<60 mL/min per 1.73 $m^2$) and each of the highest values with the lowest values for several factors (blood Cd and Pb concentration for quartile, age, education, total household income for quartile, occupation, smoking, alcohol consumption, and anemia) were determined using univariate logistic regression. Multivariate logistic regression analyses were used to determine the association between moderate-to-severe glomerular dysfunction (dependent variable) and blood Cd concentration quartiles as independent variables, after adjusting for survey years, age, and other confounders by gender. Model I used multivariate logistic analysis after adjusting for survey years and age, whereas Model II used multivariate logistic regression after adjusting for Model I and potential confounders (blood Pb concentration for quartiles, age, education, total household income for quartiles, occupation, smoking, alcohol consumption, and anemia), comparing each of the three highest quartiles of Cd in blood with the lowest quartile.

## Results

The geometric means of blood Cd levels were higher in categories that included women, higher blood lead quartiles, older age, less educated, less total house income, current smoker, drinking alcohol less than once per month, and with anemia, compared with those not in any of these categories. The mean eGFR was higher in categories that included younger age, manual workers, men, participants with lowest quartile of blood Cd and Pb, and drinking alcohol more than once per month (Table 1).

Female subjects in the highest quartile of blood Cd and Pb levels had a prevalence of moderate-to-severe glomerular dysfunction ≥3-fold higher than those in the lowest

**Table 1** Geometric mean and 95% confidence interval of blood cadmium concentration (μg/L) and mean and 95% confidence interval of estimated GFR (mL/min per 1.73 m$^2$) in a Korean population, aged between 20 and 65

| | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cadmium | | | eGFR[a] | | Cadmium | | | eGFR[a] | |
| | *n* | GM[b] | 95% CI | Mean | 95% CI | *n* | GM[b] | 95% CI | Mean | 95% CI |
| Blood cadmium | | | | | | | | | | |
| 1Q (lowest) | 353 | 0.49 | 0.21–0.78 | 67.7 | 50.9–92.1 | 396 | 0.52 | 0.23–0.78 | 68.7 | 49.4–99.5 |
| 2Q | 345 | 1.00 | 0.82–1.19 | 65.2 | 48.5–84.7 | 395 | 1.01 | 0.83–1.19 | 62.2 | 44.9–83.2 |
| 3Q | 355 | 1.45 | 1.25–1.70 | 64.5 | 50.1–81.3 | 397 | 1.45 | 1.23–1.69 | 59.0 | 44.5–80.6 |
| 4Q (highest) | 356 | 2.28 | 1.77–3.24 | 64.0 | 49.3–78.4 | 395 | 2.33 | 1.76–3.74 | 57.1 | 44.1–75.7 |
| Blood lead | | | | | | | | | | |
| 1Q (lowest) | 355 | 0.93 | 0.25–2.78 | 67.8 | 52.1–90.8 | 393 | 1.00 | 0.30–2.61 | 66.2 | 40.0–91.1 |
| 2Q | 349 | 1.01 | 0.35–2.85 | 66.0 | 49.3–85.5 | 400 | 1.13 | 0.41–2.60 | 63.8 | 45.9–89.6 |
| 3Q | 352 | 1.19 | 0.42–2.72 | 64.8 | 50.2–81.3 | 394 | 1.25 | 0.47–2.72 | 60.5 | 45.6–82.0 |
| 4Q (highest) | 353 | 1.30 | 0.52–2.69 | 62.6 | 48.4–77.8 | 396 | 1.38 | 0.58–3.25 | 56.6 | 43.7–76.3 |
| Age | | | | | | | | | | |
| 20–29 | 295 | 0.84 | 0.23–2.50 | 74.5 | 59.2–95.2 | 345 | 0.83 | 0.25–2.31 | 72.6 | 55.1–99.5 |
| 30–39 | 376 | 1.13 | 0.37–2.78 | 66.6 | 54.3–81.3 | 419 | 1.12 | 0.45–2.42 | 63.5 | 50.5–88.9 |
| 40–49 | 353 | 1.17 | 0.41–2.64 | 62.3 | 48.5–80.4 | 371 | 1.36 | 0.56–2.94 | 58.8 | 47.2–82.5 |
| 50–59 | 279 | 1.18 | 0.44–2.74 | 61.0 | 46.9–78.4 | 322 | 1.44 | 0.63–3.17 | 54.7 | 44.5–68.9 |
| 60–65 | 105 | 1.39 | 0.51–2.68 | 56.6 | 41.5–74.7 | 125 | 1.45 | 0.64–3.36 | 52.6 | 43.3–75.7 |
| Education | | | | | | | | | | |
| Elementary | 140 | 1.30 | 0.48–2.80 | 62.9 | 49.3–78.2 | 281 | 1.52 | 0.63–3.36 | 55.7 | 43.3–77.8 |
| Middle school | 144 | 1.22 | 0.51–2.62 | 62.2 | 45.4–80.1 | 186 | 1.37 | 0.61–2.91 | 57.6 | 44.5–79.8 |
| High school | 615 | 1.07 | 0.31–2.60 | 66.4 | 50.6–86.4 | 679 | 1.15 | 0.41–2.72 | 63.0 | 46.6–87.2 |
| College | 500 | 1.04 | 0.32–2.69 | 65.6 | 51.4–83.7 | 433 | 0.97 | 0.29–2.35 | 65.6 | 49.0–91.1 |
| Total household income | | | | | | | | | | |
| 1Q (lowest) | 167 | 1.15 | 0.29–2.60 | 65.3 | 49.8–85.5 | 240 | 1.34 | 0.51–3.17 | 58.3 | 43.5–79.0 |
| 2Q | 351 | 1.18 | 0.41–2.78 | 65.6 | 48.2–84.7 | 432 | 1.18 | 0.45–2.59 | 62.2 | 45.4–83.5 |
| 3Q | 396 | 1.13 | 0.37–2.78 | 65.8 | 51.1–85.5 | 442 | 1.17 | 0.42–2.91 | 62.4 | 45.6–88.9 |
| 4Q (highest) | 465 | 1.01 | 0.30–2.56 | 64.8 | 50.1–82.8 | 444 | 1.11 | 0.35–2.52 | 62.5 | 45.6–86.4 |
| Occupation[c] | | | | | | | | | | |
| Manual | 258 | 0.91 | 0.29–2.45 | 67.1 | 49.8–87.4 | 137 | 1.20 | 0.47–3.16 | 63.7 | 47.8–88.9 |
| Other | 1,151 | 1.14 | 0.35–2.70 | 64.9 | 49.6–83.7 | 1,446 | 1.18 | 0.41–2.81 | 61.5 | 44.9–84.6 |
| Smoker | | | | | | | | | | |
| Non-smoker | 300 | 0.84 | 0.23–2.59 | 66.8 | 49.8–90.8 | 1,430 | 1.17 | 0.42–2.76 | 61.3 | 44.8–84.1 |
| Ex-smoker | 455 | 1.08 | 0.36–2.60 | 63.1 | 47.1–79.9 | 63 | 1.11 | 0.22–2.92 | 65.6 | 49.4–98.4 |
| Current smoker | 654 | 1.26 | 0.48–2.78 | 66.2 | 51.7–85.5 | 90 | 1.34 | 0.49–3.17 | 66.4 | 46.6–100.7 |
| Drinking[d] | | | | | | | | | | |
| No | 405 | 1.08 | 0.34–2.78 | 64.7 | 49.3–82.8 | 923 | 1.22 | 0.46–2.81 | 60.3 | 44.4–83.0 |
| Yes | 1,004 | 1.11 | 0.35–2.62 | 65.6 | 50.1–85.5 | 660 | 1.13 | 0.38–2.85 | 63.7 | 46.6–88.9 |
| Anemia[e] | | | | | | | | | | |
| No | 1,380 | 1.10 | 0.34–2.68 | 65.4 | 49.8–85.5 | 1,344 | 1.17 | 0.41–2.81 | 61.7 | 44.9–85.2 |
| Yes | 26 | 1.11 | 0.48–1.93 | 59.8 | 40.9–76.8 | 236 | 1.23 | 0.45–2.91 | 62.0 | 46.9–84.1 |
| Total | 1,409 | 1.10 | 0.34–2.67 | 65.3 | 49.8–85.3 | 1,583 | 1.18 | 0.42–2.83 | 61.7 | 44.9–85.1 |

Blood cadmium quartiles: for men (μg/L) 1Q: Cd < 0.75; 2Q: 0.75 ≤ Cd < 1.19; 3Q: 1.19 ≤ Cd < 1.72; and 4Q: Cd ≥ 1.72. For women (μg/L) 1Q: Cd < 0.85; 2Q: 0.85 ≤ Cd < 1.23; 3Q: 1.23 ≤ Cd < 1.74; and 4Q: Cd ≥ 1.74

Blood lead quartiles: for men (μg/dL) 1Q: Pb < 2.23; 2Q: 2.23 ≤ Pb < 2.91; 3Q: 2.91 ≤ Pb < 3.88; and 4Q: Pb ≥ 3.88. For women (μg/L) 1Q: Pb < 1.55; 2Q: 1.55 ≤ Pb < 2.15; 3Q: 2.15 ≤ Pb < 2.88; and 4Q: Pb ≥ 2.88

[a] Estimated glomerular filtration rate (eGFR) was calculated with the equation from the Modification of Diet in Renal Disease Study for Japanese

[b] Geometric mean

[c] Manual workers included agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and elementary occupations; "other" included non-manual workers and those who were not in the labor market

[d] Less than once per month (no); more than once per month (yes)

[e] Anemia was defined as hemoglobin below 12 g/dL for non-pregnant women, 11 g/dL for pregnant women, and 13 g/dL for men

quartile. Female subjects with the lowest education and quartile of total household income had a prevalence of moderate-to-severe glomerular dysfunction that was 4.7- and 1.9-fold higher than subjects with higher education and a quartile of total household income, respectively. In contrast, female manual workers, current smokers, and drinkers had a lower prevalence of moderate-to-severe glomerular dysfunction than other workers, non-smokers, and non-drinkers (less than once per month). Based on trends in ORs, a relatively increasing trend in the higher quartiles of blood Cd was seen in women, but not in men (Table 2).

Survey years and age-adjusted odds ratios of moderate-to-severe glomerular dysfunction were associated with blood Cd quartiles in Model I (Table 3). The odds ratios comparing the second, third, and fourth quartile versus the first quartile (lowest) in women were 1.20 (95% confidence interval (CI): 0.83–1.75), 1.95 (95% CI: 1.31–2.90), and 2.26 (95% CI: 1.48–3.46) in Model I, respectively. Even after adjusting Model I for potential confounders (blood Pb concentration by quartile, age, education, total household income by quartile, occupation, smoking, alcohol consumption, and anemia), the odds ratio of moderate-to-severe glomerular dysfunction was significantly higher [OR 2.48 (95% CI: 1.74–3.54)] in the fourth quartile of Cd in women (Table 3).

## Discussion

The geometric means of the blood Cd levels of men (1.10 μg/L) and women (1.18 μg/L) were lower in this study than in a previous field study of Korean subjects (Moon et al. 1995). The geometric mean of the blood Cd levels of participants in this study was higher than participants in the US general population and Swedish women, 0.41 μg/L and 0.38 μg/L, respectively (Navas-Acien et al. 2009; Akesson et al. 2005), but lower than those in the Japanese and Chinese general population (Jin et al. 2002; Ikeda et al. 2000). According to several studies, blood Cd levels are higher in Korea, Japan, and China (northeast Asia), where rice is a major food, compared with Western countries (Jarup and Akesson 2009; Jarup et al. 1998; Nordberg et al. 2007), where it is not. A polished rice diet, which is of poor nutritional quality (deficient in zinc and iron) can cause marginal deficiency in these essential metals, and this dietary pattern can enhance intestinal Cd absorption (Reeves and Chaney 2008). Furthermore, a high concentration of Cd has been observed in seafood, including fish, mollusks, and crustaceans, that are popular in the diet in these Asian countries (Vahter et al. 1996). A study on dietary Cd intake in South Korea showed that seafood accounted for 40% of the average total daily dietary Cd (Kim and Wolt 2011). These dietary factors may give rise to higher blood Cd levels in Koreans versus those in Western subjects.

Recent reports suggest that decreased GFR may occur with low-dose Cd exposure (environmentally exposed population) (Akesson et al. 2005; Suwazono et al. 2006; Navas-Acien et al. 2009). In a population-based women's health survey in southern Sweden ($n = 820$), Cd in blood (median, 0.38 μg/L) was significantly associated with GFR after adjusting for other covariables (regression coefficients: −4.3, 95% CI: −6.6 to −1.9, $R^2 = 0.15$) (Akesson et al. 2005). According to research on blood Cd and glomerular dysfunction, an association between blood Cd and moderate-to-severe glomerular dysfunction (<60 mL/min per 1.73 $m^2$) has been suggested in US adults (Navas-Acien et al. 2009). The odds ratio for moderate-to-severe glomerular dysfunction comparing the highest versus lowest blood Cd was 1.32 (95% CI: 1.04–1.68) (Navas-Acien et al. 2009). In our study, participants in the higher quartiles of blood Cd levels were likely to have decreased eGFR in the representative sample of Koreans examined, aged between 20 and 65. The odds ratio for the prevalence of decreased eGFR in highest quartile of blood Cd levels versus the lowest was 1.58 in the multiple logistic regression, and this result was more prominent in women.

Several studies have shown that the concentration of Cd in blood and in urine is higher in women than men (Berglund et al. 1994; Kippler et al. 2007; Akesson et al. 2002), but the reason remains unknown. A possible mechanism is a difference in the kinetics of Cd. Iron-deficient animals may have higher absorption of Cd, as seen in an animal study (Hamilton and Valberg 1974). According to a study on the association between the concentration of Cd in blood and iron storage in a Swedish population, women showed higher concentrations of Cd in blood than men, who had higher iron storage, and there was an inverse relationship between the concentration of serum ferritin and blood Cd (Berglund et al. 1994). No women with serum ferritin of 30 μg/L or more showed a blood Cd level over 0.3 μg/L (Berglund et al. 1994). This difference in the Cd kinetics may suggest that reduced iron storage in the body may give rise to increased absorption of dietary Cd. Our results showed that blood Cd concentrations in subjects with anemia were higher than in those without anemia.

In our study, the association between blood cadmium levels and moderate-to-severe glomerular dysfunction was greater in women than men. Several epidemiological reports have shown susceptibility to renal dysfunction in women (Navas-Acien et al. 2009; Kido et al. 1991). A study on the association between heavy metals and glomerular dysfunction in the US general population showed that the odds ratio of moderate-to-severe glomerular dysfunction (<60 mL/min per 1.73 $m^2$) was 1.35 (95% CI: 1.12–1.64) in women but 1.16 (95% CI: 0.95–1.42) in men

**Table 2** Prevalence (95% confidence intervals) and odds ratios for moderate-to-severe glomerular dysfunction (<60 mL/min per 1.73 m$^2$)

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | *n* (%) | OR | 95% CI | *n* (%) | OR | 95% CI |
| Blood cadmium | | | | | | |
| 1Q (lowest) | 100 (28.3) | Reference | | 123 (31.1) | Reference | |
| 2Q | 110 (31.9) | 1.18 | 0.86–1.64 | 189 (47.9) | 2.04 | 1.53–2.73 |
| 3Q | 120 (33.8) | 1.29 | 0.94–1.78 | 237 (59.7) | 3.29 | 2.46–4.41 |
| 4Q (highest) | 117 (32.9) | 1.27 | 0.90–1.71 | 269 (68.1) | 4.74 | 3.52–6.42 |
| *p* for trend | | 0.1580 | | | <0.0001 | |
| Blood lead | | | | | | |
| 1Q (lowest) | 95 (26.8) | Reference | | 147 (37.4) | Reference | |
| 2Q | 109 (31.2) | 1.24 | 0.90–1.72 | 179 (44.8) | 1.36 | 1.02–1.80 |
| 3Q | 118 (33.5) | 1.38 | 1.00–1.91 | 217 (55.1) | 2.05 | 1.55–2.73 |
| 4Q (highest) | 125 (35.4) | 1.50 | 1.09–2.07 | 275 (69.4) | 3.80 | 2.84–5.13 |
| *p* for trend | | 0.0114 | | | <0.0001 | |
| Age | | | | | | |
| 20–29 | 24 (8.1) | Reference | | 58 (16.8) | Reference | |
| 30–39 | 82 (21.8) | 3.15 | 1.97–5.21 | 190 (45.4) | 4.11 | 2.93–5.81 |
| 40–49 | 150 (42.5) | 8.34 | 5.32–13.60 | 202 (54.5) | 5.91 | 4.20–8.43 |
| 50–59 | 104 (37.3) | 6.71 | 4.21–11.09 | 262 (81.4) | 21.60 | 14.63–32.45 |
| 60–65 | 87 (82.9) | 54.58 | 29.00–108.35 | 106 (84.8) | 27.60 | 16.04–49.76 |
| *p* for trend | | <0.0001 | | | <0.0001 | |
| Education | | | | | | |
| Elementary | 52 (37.1) | 1.41 | 0.95–2.08 | 212 (75.4) | 4.66 | 3.36–6.54 |
| Middle school | 61 (42.4) | 1.75 | 1.19–2.56 | 123 (66.1) | 2.96 | 2.08–4.26 |
| High school | 181 (29.4) | 0.99 | 0.77–1.29 | 308 (45.4) | 1.26 | 0.99–1.61 |
| College | 148 (29.6) | Reference | | 172 (39.7) | Reference | |
| *p* for trend | | 0.0109 | | | <0.0001 | |
| Total household income | | | | | | |
| 1Q (lowest) | 63 (37.7) | 1.29 | 0.89–1.85 | 157 (65.4) | 1.91 | 1.38–2.65 |
| 2Q | 106 (30.2) | 0.92 | 0.68–1.24 | 214 (49.5) | 0.99 | 0.76–1.29 |
| 3Q | 115 (29.0) | 0.97 | 0.65–1.16 | 212 (48.0) | 0.93 | 0.71–1.21 |
| 4Q (highest) | 149 (32.0) | Reference | | 221 (49.8) | Reference | |
| *p* for trend | | 0.4450 | | | <0.0001 | |
| Occupation[a] | | | | | | |
| Manual | 71 (27.5) | 0.78 | 0.58–1.05 | 64 (46.7) | 0.81 | 0.57–1.14 |
| Other | 376 (32.7) | Reference | | 754 (52.1) | Reference | |
| Smoker | | | | | | |
| Non-smoker | 93 (31.0) | Reference | | 759 (53.1) | Reference | |
| Ex-smoker | 172 (37.8) | 1.53 | 0.99–1.85 | 23 (36.5) | 0.51 | 0.30–0.85 |
| Current smoker | 182 (27.8) | 0.86 | 0.64–1.56 | 36 (40.0) | 0.59 | 0.38–0.91 |
| *p* for trend | | 0.0930 | | | 0.0018 | |
| Drinking[b] | | | | | | |
| No | 138 (34.1) | Reference | | 522 (56.6) | Reference | |
| Yes | 309 (30.8) | 0.86 | 0.67–1.10 | 296 (44.9) | 0.63 | 0.51–0.76 |
| Anemia[c] | | | | | | |
| No | 434 (31.5) | Reference | | 698 (51.9) | Reference | |
| Yes | 13 (50.0) | 2.18 | 0.99–4.79 | 119 (50.4) | 0.94 | 0.71–1.24 |

Blood cadmium quartiles: for men (μg/L) 1Q: Cd < 0.75; 2Q: 0.75 ≤ Cd < 1.19; 3Q: 1.19 ≤ Cd < 1.72; and 4Q: Cd ≥ 1.72. For women (μg/L) 1Q: Cd < 0.85; 2Q: 0.85 ≤ Cd < 1.23; 3Q: 1.23 ≤ Cd < 1.74; and 4Q: Cd ≥ 1.74

Blood lead quartiles: for men (μg/dL) 1Q: Pb < 2.23; 2Q: 2.23 ≤ Pb < 2.91; 3Q: 2.91 ≤ Pb < 3.88; and 4Q: Pb ≥ 3.88. For women (μg/L) 1Q: Pb < 1.55; 2Q: 1.55 ≤ Pb < 2.15; 3Q: 2.15 ≤ Pb < 2.88; and 4Q: Pb ≥ 2.88

[a] Manual workers included agriculture, forestry, fishery workers, craft and related trade workers, plant and machine operators and assemblers, and elementary occupations; "other" included non-manual workers and those who were not in the labor market

[b] Less than once per month (no); more than once per month (yes)

[c] Anemia was defined as hemoglobin below 12 g/dL for non-pregnant women, 11 g/dL for pregnant women, and 13 g/dL for men

(Navas-Acien et al. 2009). In a Japanese study on Cd exposure and renal dysfunction in the general population aged 50 or older, the prevalence rates of metallothioneinuria, reflecting renal dysfunction, with cadmium toxicity were 3.1% in women versus 1.8% in men (Kido et al. 1991). However, those studies were unable to definitely explain the phenomenon. In these gender differences in Cd-associated renal dysfunction, MT is likely to play an important

**Table 3** Age-adjusted (Model I) and Model I plus other factors-adjusted (Model II) OR (95% CI) for moderate-to-severe glomerular dysfunction, comparing the first quartile and the fourth quartile of blood cadmium levels by gender

| | Model I | | | | Model II | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Blood cadmium | | | | | | | | |
| 1Q (lowest) | Reference | | Reference | | Reference | | Reference | |
| 2Q | 0.90 | 0.59–1.37 | 1.20 | 0.83–1.75 | 0.88 | 0.61–1.29 | 1.18 | 0.84–1.66 |
| 3Q | 0.81 | 0.54–1.22 | 1.95 | 1.31–2.90 | 0.91 | 0.62–1.34 | 1.79 | 1.27–2.53 |
| 4Q (highest) | 0.77 | 0.50–1.19 | 2.26 | 1.48–3.46 | 0.74 | 0.50–1.10 | 2.48 | 1.74–3.54 |

Model I: adjusted by survey years and age

Model II: adjusted by Model I + education, occupation, household income, smoke, alcohol, anemia, and blood lead levels

role. With effective MT synthesis, the influx of Cd-MT complexes into the lysosomes and "free" cadmium ions are limited, and no membrane damage occurs (Jarup et al. 1998). According to an animal study, 17 beta-estradiol and progesterone can reduce MT-I mRNA expression in ovariectomized mice, and more MT-I mRNA expression is seen in male than female mice (Sogawa et al. 2001). Thus, it is possible that a sex hormone may play an important role in MT synthesis. However, MT in kidney did not seem to depend on gender in a human study (Drasch et al. 1988), so this remains unclear. Further population-based and experimental studies are needed to characterize susceptibility to cadmium-associated glomerular dysfunction in women.

Blood Cd was used as a biomarker for environmental Cd exposure in this study, whereas urinary Cd has been used in other studies. Blood Cd is considered the most valid marker of recent exposure (Berglund et al. 1994). There are two half-lives for Cd; one is the fast component, with a half-life of 3–4 months, and the other is the slow component, with a half-life of 7–16 years (Jarup et al. 1983). The slow component is due to chronic Cd body accumulation (life-time body burden) released into the blood. After long-term environmental Cd exposure, blood Cd levels may be a good reflection of the Cd body burden (Jarup and Akesson 2009; Jarup et al. 1998).

Accumulation of life-long cadmium can give rise to an increase in blood Cd levels with age (Berglund et al. 1994; Elinder et al. 1983; Jarup et al. 1998). These studies showed that seniors had higher Cd concentrations in blood than did younger adults. GFR also decreases gradually with age, with a maximum level of GFR at around 25 years of age (Jarup and Akesson 2009; Jarup et al. 1998); in that study, the authors tried to reduce this bias by restricting the age to 65 years or younger. We also adjusted for age in the multivariate analyses, but even after adjusting for age, moderate-to-severe glomerular dysfunction was associated with blood Cd quartiles.

Our study has some limitations because it was a cross-sectional survey study, so we could not evaluate any causal relationship between blood Cd levels and glomerular dysfunction. However, despite the lack of longitudinal data for environmental Cd exposure, recent reports have suggested that decreased GFR and creatinine clearance may occur in populations with low-level Cd exposure (Suwazono et al. 2006; Akesson et al. 2005; Kobayashi et al. 2008).

An inverse association between Cd and renal function may be possible. In the US general population, however, moderate-to-severe glomerular dysfunction does not reduce the clearance of cadmium, because renal Cd loss continues even when renal toxicity is present (Nordberg et al. 2007; Jarup et al. 1998). Additionally, although lead binds to high-molecular weight plasma albumin, cadmium binds to MT, a small polypeptide that is readily filtered through the glomerulus (Lewis et al. 1972). These facts suggest that a simple inverse association is less likely. We estimated eGFR based on the MDRD study equation. Thus, our results may underestimate the adverse health effects of Cd due to the known limitations of eGFR as a marker of kidney damage (Poggio and Rule 2007; Rule et al. 2004). However, this equation is widely used for estimating GFR in epidemiological studies (Navas-Acien et al. 2009; Jang et al. 2010). Our results were derived from two laboratories, which may also have resulted in variation and subsequent detection errors during measurement. However, both laboratories underwent internal and external quality control and were certified by the Korean Ministry of Health and Welfare. Due to limited information in our survey data, some potential confounders (microalbuminuria, food consumption, environmental tobacco smoke, and biomarkers of other metals) could not be investigated.

A strength of this study was its large sample size, enabling us to evaluate the relationship between environmental Cd exposure and glomerular dysfunction in a general population. Another strength, compared with a previous US study (Navas-Acien et al. 2009) was that those who had been diagnosed with hypertension, diabetes, or kidney disease were excluded from this study. Hypertension and diabetes are well known as not only risk factors for renal dysfunction, but are also potential confounders in this study. Another strength is that KNHANES includes a representative sample of all non-institutionalized Korean civilians and includes extensive quality control and standardized laboratory procedures. Furthermore, this study enabled us to compare blood Cd levels in the general population with other countries due to its representativeness.

In conclusion, we found an association between Cd concentration in blood and moderate-to-severe glomerular dysfunction in Korean women. This study provides important evidence that environmental Cd exposure may potentially be associated with nephrotoxicity in women. Thus, environmental heavy metal monitoring and an institutional strategy should be implemented to reduce Cd exposure in the general population, particularly in women.

**Conflict of interest** None.

**Ethics approval** The survey data were made publicly available, and ethics approval was not needed.

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