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Effects of Exposure to Lead and Cadmium on Health of Inhabitants of Abandoned Metal Mine Area in Korea

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Abstract

People living near abandoned mines are at increased risk of exposure to toxic metals. We surveyed 4500 inhabitants with the mean age of 68.5 years old (male: 1768, female: 2732) living near 104 abandoned metal mines from 2013 to 2017 (the 2nd phase health survey in Korea). We conducted personal interviews, blood and urine sampling, and analyzed the concentrations of lead (Pb) and cadmium (Cd) in whole blood and Cd in urine using a graphite furnace atomic absorption spectrometer. The geometric means of blood Pb, blood Cd, and urine Cd were 2.27 μg/dL, 1.42 μg/L, and 1.66 μg/g creatinine, respectively. The level of metal exposure was lower than that reported from the first phase health survey in Korea (2008−2011) but was higher than in the general population of Korea. Blood Pb was higher in males while blood Cd and urine Cd were significantly higher in females. Blood Pb was highest in the 40−59 age group, while blood and urine Cd levels continuously increased until age 80 or older. The Cd levels in blood and urine were affected by consumption of locally produced rice and duration of residence near abandoned mines. Furthermore, negative correlations were observed between blood Pb and blood and urine Cd levels. Additionally, 252 of the 4500 subjects exceeded the thresholds of blood Cd or urine Cd levels. Together, these findings suggest that Cd has more sustainable and adverse health effects on the abandoned mine inhabitants, who are mostly aged. Therefore, continuous biomonitoring and risk assessment to environmental health risks are necessary for environmental pollution control and health promotion.

Lead (Pb) and cadmium (Cd) are toxic metals that are nonessential in the human body (Ali and Khan 2018). Humans are usually exposed to Pb and Cd through diet and industrial activities, such as smelting, mining, battery manufacture, etc. (Wu et al. 2016). The primary exposure to Pb and Cd in the general population is through consuming plants grown in contaminated soil (Yang et al. 2018; Davodpour et al. 2019). Cd and Pb have long biological half-lives; therefore, it has been suggested that they may accumulate in the body over lifetimes and lead to adverse health effects (Sugita and Tsuchiya 1995; Åkesson et al. 2006; Akerstrom et al. 2013; Wani et al. 2015; Eom et al. 2017; Mezynska and Brzóska 2018; Mohammadi et al. 2018). Cd is classified as carcinogenic to humans (IARC Group 1) and also induces noncarcinogenic health effects. In the general population, kidneys and bones are the main target organs, and high Cd levels in the body cause renal tubule damage and/or decreased bone mineral density (Tsuchiya 1969; Åkesson et al. 2006; Akerstrom et al. 2013; Eom et al. 2017; Mezynska and Brzóska 2018). "Itai-itai" disease is a well-known historical event involving chronic Cd poisoning in Jinzu River inhabitants (Tsuchiya 1969). Environmental exposure to Pb may induce various health effects, such as reproductive and developmental toxicity, cardiovascular disease, kidney damage, blood

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toxicity, and neurological effects especially in children (Goyer 1993; Wani et al. 2015).

Although the majority of metal mines in Korea have been closed since the 1970s, contamination of the surrounding environment (such as soil, water, and crops) of abandoned mines is inevitable and eventually leads to human exposure and health effects. Several studies have reported relatively high Cd and Pb levels in the environment and in the body of inhabitants near abandoned metal mines (Ji et al. 2013; Park et al. 2014; Hong et al. 2014). Furthermore, epidemiologic studies have suggested adverse effects on human health from metal contaminants near abandoned metal mines due to increased dietary exposure through the ingestion of contaminated rice and vegetables (Park et al. 1998; Kim et al. 2008). Therefore, the concern for the health of human inhabitants living near abandoned metal mines has gradually increased in Korea. In addition, the majority of inhabitants are elderly people who are particularly sensitive to environmental contaminants, such as metals (Navas-Acien et al. 2009; Horiguchi et al. 2013; Bridges and Zalups 2017). Therefore, the First Health Effect Surveillance for Residents in Abandoned Metal mines (HESRAM) was conducted for 38 abandoned metal mines during 2008–2011 by the Ministry of Environment. This study found increased levels of blood Pb and blood Cd in inhabitants living near these areas (Park et al. 2014) and suggested taking continuous concerns for the abandoned metal mine area inhabitants. Following this outcome, a second HESRAM was conducted to monitor exposure levels to Pb and Cd and their related health effects for 104 abandoned metal mines during 2013–2017.

In this cross-sectional study, we evaluated human exposure levels to metals by measuring blood Pb, blood Cd, and urine Cd and determined influencing factors, such as personal habits and life-style, including consumption of locally produced rice and duration of residence as well as sex and age, of metal exposure to inhabitants of 104 abandoned metal mine areas. Further analyses were conducted on the relation between Pb and Cd and on which metal persists in the body after exposure to assess whether human exposure is different between Pb and Cd in abandoned metal mine areas. Additionally, we conducted analyses of biomarkers for kidney damage in Cd-exposed inhabitants.

Materials and Methods

Study Subjects

We conducted a cross-sectional study to evaluate Cd and Pb levels of inhabitants near abandoned metal mines. This study included 4500 inhabitants (1768 males and 2732 females) from 104 target abandoned metal mine areas distributed nationwide, including in Gangwon, Gyeonggi, Chungcheong, Jeolla, and Gyeongsang provinces, over the period of 2013–2017 (Fig. 1; Table 1). Recruited study subjects included approximately 50 healthy adults 19 years of age or older who had resided within 2 km of each target mine area for more than 10 years. Written consent was obtained from each study subject after being informed about the study aim, process, and details, which was followed by a personal interview and blood and urine sampling. The study protocol was approved by the Chung-Ang Institutional Review Board.

Personal Interviews and Blood and Urine Sampling

Personal interviews were conducted by trained personnel using a standardized questionnaire, which contained information on demographic characteristics of study subjects, such as age, smoking habit, alcoholic drinking, duration of residence, occupational history of mining, and monthly income and asked whether rice consumption included more than 50% locally produced rice. Whole blood was sampled by an experienced nurse under the observation of a doctor using a metal-free blood collection tube containing EDTA for trace metals analysis. Spot urine was sampled. Overall, 4489 blood and 2668 urine samples were collected from the study subjects; urine was not sampled in 2013 and 2014. Blood and urine samples were stored at − 80 °C until analysis. Study subjects who exceeded the guideline levels of Cd in blood (5 μg/L) or urine (5 μg/g creatinine) participated in

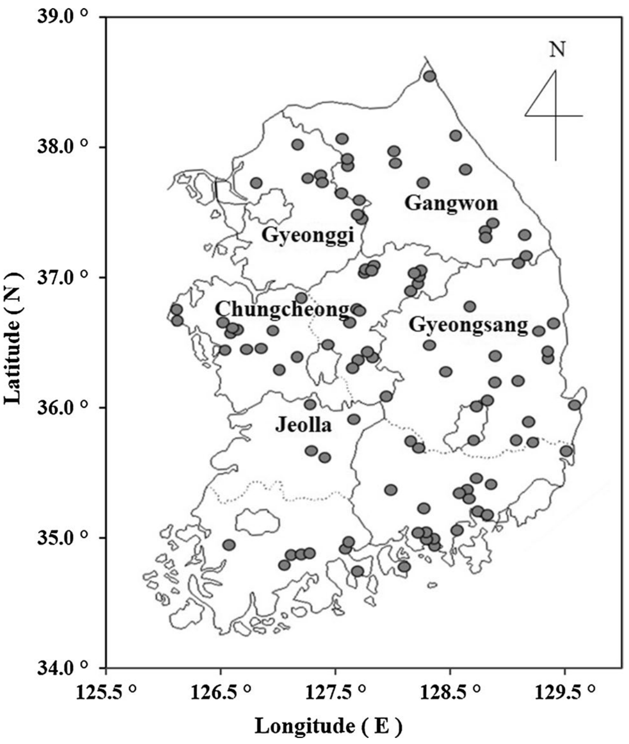

Fig. 1 Distribution of 104 target abandoned metal mines

Table 1 Distribution of subjects in abandoned metal mine areas according to epidemiological characteristics

Characteristics	Male *N* (%)	Female *N* (%)	Total *N* (%)
District			
Gangwon	282 (16.0%)	349 (12.8%)	631 (14.0%)
Gyeonggi	115 (6.5%)	157 (5.7%)	272 (6.1%)
Chungcheong	571 (32.3%)	838 (30.7%)	1409 (31.3%)
Jeolla	211 (11.9%)	410 (15.0%)	621 (13.8%)
Gyeongsang	589 (33.3%)	978 (35.8%)	1567 (34.8%)
Age (yr)			
≤ 39	37 (2.1%)	32 (1.2%)	69 (1.5%)
40–59	364 (20.6%)	514 (18.8%)	878 (19.5%)
60–79	1154 (65.3%)	1692 (61.9%)	2846 (63.3%)
≥ 80	213 (12.0%)	493 (18.1%)	706 (15.7%)
Mean ± SD	67.2 ± 11.7	69.4 ± 11.4	68.5 ± 11.6
Duration of residence (yr)			
− 19	321 (18.2%)	442 (16.2%)	763 (17.0%)
20–39	199 (11.3%)	505 (18.6%)	704 (15.7%)
40–	1240 (70.5%)	1774 (65.2%)	3014 (67.3%)
Mean ± SD	50.0 ± 25.1	43.6 ± 20.9	46.1 ± 22.8
Smoking			
Nonsmokers	590 (33.4%)	2603 (95.5%)	3193 (71.1%)
Smokers	1178 (66.6%)	123 (4.5%)	1301 (28.9%)
Alcoholic drinking			
Nondrinkers	485 (27.5%)	1818 (67.0%)	2303 (51.4%)
Drinkers	1280 (72.5%)	897 (33.0%)	2177 (48.6%)
Working history			
No	1356 (78.2%)	2474 (92.8)	3830 (87.0%)
Yes	377 (21.8%)	193 (7.2%)	570 (13.0%)
Income (US $/month)			
< 850	1200 (67.9%)	2252 (82.5%)	3452 (76.8%)
850–1699	322 (18.2%)	277 (10.1%)	599 (13.3%)
≥ 1700	246 (13.9%)	201 (7.4%)	447 (9.9%)
Rice consumption[a]			
< 50%	799 (45.3%)	1460 (53.5%)	2259 (50.3%)
≥ 50%	966 (54.7%)	1269 (46.5%)	2235 (49.7%)
Total	1768 (39.3%)	2732 (60.7%)	4500 (100.0%)

[a] Proportion of locally produced rice consumption to that of total rice consumption

the subsequent study on renal effects, such as N-acetyl-ß-D-glucosaminidase (NAG), ß$_2$-microglobulin (ß$_2$-MG), and the estimated glomerular filtration rate (eGFR).

Determination of Heavy Metals in Whole Blood and Urine

The concentrations of blood Pb, blood Cd, and urine Cd were analyzed using a graphited atomic absorption spectrophotometer with a flameless method (Hitachi Z-2700, Japan for blood Pb; Varian SpecrAA240Z, Australia for blood Cd and urine Cd). Briefly, whole blood was diluted in 0.5% ammonium dihydrogen phosphate and 1.0% Triton X-100 for Pb and in 0.2% Triton X-100 and 1.0% nitric acid for Cd. Urine was diluted in 0.2% Triton X-100 and 1.0% nitric acid. Diluted samples (15 µL) were placed into the graphite tube. The limits of detection were 0.20 µg/dL for blood Pb, 0.10 µg/L for blood Cd, and 0.03 µg/L for urine Cd. Creatinine concentration in diluted urine was determined by reaction with picric acid and NaOH by the colorimetric method using a microplate reader (Spectra 340) with Jaffe reaction (Bonsnes and Taussky 1945).

Measurement of ß$_2$-Microglobulin and N-Acetyl-ß-D-Glucosaminidase Activity

Levels of ß$_2$-MG and NAG activity in urine were measured as biomarkers for renal tubular damage. The ß$_2$-MG concentrations in urine were analyzed using a ß$_2$-MG Elisa kit (Immundiagnostik, Germany), and NAG activity was analyzed by using NAG quantitative kit (Shionogi, Osaka, Japan) according to the manufacturer's procedures. The eGFR was calculated using the Modification of Diet in Renal Disease formula $[\text{eGFR} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742\,(\text{female})]$ (Levey et al. 1999). Creatinine concentration in diluted serum was determined by reaction with picric acid and NaOH by the colorimetric method using a microplate reader (Spectra 340) with Jaffe reaction (Bonsnes and Taussky 1945).

Statistical Analyses

Statistical analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC). The concentrations of blood Pb, blood Cd, and urine Cd were log-transformed for statistical analyses, because log-transformed values of these metals are better fit with a normal distribution than measured values. The comparison of means was performed by Students' *t* test, one sample *t* test, or ANOVA following multiple comparison tests by Duncan's method. The relationships among Pb in blood, Cd in blood, and Cd in urine were analyzed by Spearman's rank correlation analysis. The factors contributing to the Pb and Cd levels in the abandoned metal mine area inhabitants were determined by multiple regression analyses. "High NAG" was defined as > 11.5 U/g creatinine and "High ß$_2$-MG" as > 300 µg/g creatinine (Roels et al. 1989). "Low eGFR" was defined as < 60 mL/min/1.73 m^2 (Levey et al. 1999). Statistical significance was set at $p < 0.05$ or $p < 0.01$.

Results

Demographic distributions of study subjects are presented in Table 1. By district, the number of study subjects was the highest in the Gyeongsang area at 34.8% of total subjects, followed by Chungcheong, Gangwon, Jeolla, and Gyeonggi. The mean age of study subjects was 68.5 years, and there was a similar distribution by age group between males and females. The mean duration of residence was 46.1 years, and approximately 83% of study subjects had resided in the area for more than 20 years. Smoking and alcoholic drinking were more common in males than in females. Of the study subjects, 13.0% had an occupational history in metal mines, and 76.8% had a monthly income of < US $850. The number of residents whose total rice consumption consisted of more than 50% locally produced rice was similar to the number whose consumption was less than 50% (Table 1).

The geometric mean (GM) concentration of blood Pb in study subjects was 2.27 µg/dL, which was significantly higher in males (2.71 µg/dL) than in females (2.03 µg/dL). The arithmetic mean (AM), median, and 95th percentile of blood Pb concentrations were 2.51 µg/dL, 2.25 µg/dL, and 4.72 µg/dL, respectively. The GMs of Cd concentrations in blood and urine were 1.42 µg/L and 1.66 µg/g creatinine, respectively, which were higher in females (1.60 µg/L and 2.13 µg/g creatinine, respectively) than in males (1.18 µg/L and 1.13 µg/g creatinine, respectively). The AMs, medians, and 95th percentiles of Cd concentrations were 1.69 µg/L, 1.40 µg/L, and 3.79 µg/L, respectively, in blood and 2.26 µg/g creatinine, 1.73 µg/g creatinine, and 5.81 µg/g creatinine, respectively, in urine (Table 2).

The blood Pb concentrations were the highest in the 40- to 59-year-old subjects and tended to decrease in old age groups in both males and females. However, the Cd concentrations in blood and urine increased in an age-dependent pattern until age 80 years and older. Blood and urine Cd levels, but not in blood Pb, increased with increasing duration of residence. The levels of Pb and Cd were significantly higher in smokers than in nonsmokers. Blood Pb levels were higher in alcohol drinkers than in non-drinkers in both males and females. Although there were no observed remarkable differences in Cd levels of blood or urine by alcohol drinking habits in males, Cd levels were higher in female nondrinkers than in female drinkers. Males with an occupational history in metal mines had higher blood Pb levels than those without, and females who formally worked in metal mines had higher blood Cd levels than those who did not. The Cd concentrations in blood and urine were higher in subjects with lower monthly incomes and were higher in those for whom total rice consumption included more than 50% locally produced rice. Conversely, blood Pb was not significantly different by monthly income or consumption of locally produced rice (Table 3). Based on multiple regression analyses, contributing factors to blood Pb levels were smoking, alcoholic drinking, and a history of working in metal mines in males and alcoholic drinking in females. Age, duration of residence, smoking, consumption of locally produced rice, and monthly income were determined to be contributing factors to blood Cd levels in both males and females. In urine Cd, contributing factors were age, smoking, and consumption of locally produced rice in males and age, duration of residence, and consumption of locally produced rice in females (Table 4). A highly significant positive relation was observed between blood Cd and urine Cd ($r = 0.5200$, $p < 0.01$), whereas blood Pb was statistically negatively correlated with blood Cd and urine Cd ($p < 0.01$) (Table 5; Fig. 2).

Approximately 1.8% (80/4489) and 6.9% (185/2668) of study subjects had blood Cd or urine Cd levels,

Table 2 Mean concentrations of metals in blood and urine of study subjects

Metals	Sex	*N*	Mean ± SD	GM (GSD)	Range (min–max)	Percentile				
						25th	50th	75th	90th	95th
Blood Pb (µg/dL)	Male	1761	2.97 ± 1.48**	2.71 (1.53)**	(0.59–21.99)	2.06	2.69	3.51	4.62	5.41
	Female	2724	2.21 ± 1.00	2.03 (1.49)	(0.49–11.54)	1.55	2.01	2.61	3.34	3.91
	Total	4485	2.51 ± 1.27	2.27 (1.54)	(0.49–21.99)	1.69	2.25	3.00	3.93	4.72
Blood Cd (µg/L)	Male	1761	1.40 ± 0.90	1.18 (1.79)	(0.14–9.59)	0.80	1.19	1.75	2.45	2.92
	Female	2728	1.89 ± 1.25**	1.60 (1.76)**	(0.19–17.95)	1.09	1.56	2.33	3.25	4.07
	Total	4489	1.69 ± 1.15	1.42 (1.80)	(0.14–17.95)	0.97	1.40	2.10	2.99	3.79
Urine Cd (µg/g creatinine)	Male	1061	1.53 ± 1.77	1.13 (2.15)	(0.05–28.8)	0.74	1.16	1.83	2.75	3.63
	Female	1607	2.74 ± 2.34**	2.13 (2.06)**	(0.01–38.84)	1.41	2.16	3.30	5.03	6.92
	Total	2668	2.26 ± 2.21	1.66 (2.23)	(0.01–38.84)	1.03	1.73	2.82	4.29	5.81

AM arithmetic mean; *SD* standard deviation; *GM* geometric mean; *GSD* geometric standard deviation

**$p < 0.01$

Table 3 Geometric mean concentrations of blood Pb, blood Cd, and urine Cd according to epidemiological characteristics of study subjects

Characteristics	Blood Pb (μg/dL)		Blood Cd (μg/L)		Urine Cd (μg/g creatinine)	
	Male GM (GSD)	Female GM (GSD)	Male GM (GSD)	Female GM (GSD)	Male GM (GSD)	Female GM (GSD)
Age (yr)						
≤ 39	1.99 (1.53)^{a}	1.55 (1.48)^{a}	0.70 (1.86)^{a}	0.81 (1.70)^{a}	0.33 (3.16)^{a}	0.75 (1.90)^{a}
40–59	2.91 (1.51)^{e}	2.17 (1.46)^{b}	1.12 (1.72)^{b}	1.45 (1.67)^{b}	0.90 (1.94)^{b}	1.65 (2.20)^{b}
60–79	2.71 (1.53)^{c,d}	2.02 (1.49)^{b}	1.21 (1.78)^{b}	1.64 (1.77)^{b,c}	1.20 (2.08)^{c}	2.31 (2.01)^{c}
≥ 80	2.48 (1.49)^{b}	1.97 (1.52)^{b}	1.27 (1.82)^{b}	1.71 (1.77)^{c}	1.37 (2.30)^{c}	2.18 (1.93)^{c}
p value	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Duration of residence (yr)						
≤ 19	2.61 (1.52)	2.09 (1.51)^{b}	1.04 (1.71)^{a}	1.32 (1.66)^{a}	0.95 (2.19)^{a}	1.79 (2.12)^{a}
20–39	2.83 (1.48)	2.12 (1.46)^{b}	1.09 (1.73)^{a}	1.48 (1.69)^{b}	0.94 (2.16)^{a}	1.89 (2.07)^{a}
≥ 40	2.71 (1.54)	1.99 (1.50)^{a}	1.23 (1.80)^{b}	1.71 (1.78)^{c}	1.22 (2.12)^{b}	2.30 (2.02)^{b}
p value	NS	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Smoking						
Nonsmokers	2.54 (1.52)	2.02 (1.49)	1.05 (1.81)	1.59 (1.76)	1.05 (2.24)	2.12 (2.04)
Smokers	2.79 (1.53)**	2.20 (1.52)*	1.25 (1.76)**	1.85 (1.78)**	1.17 (2.12)*	2.31 (2.58)
p value	< 0.01	< 0.05	< 0.01	< 0.01	< 0.05	NS
Alcoholic drinking						
Nondrinkers	2.46 (1.52)	1.97 (1.50)	1.17 (1.84)	1.63 (1.77)**	1.16 (2.30)	2.22 (2.01)**
Drinkers	2.80 (1.52)**	2.16 (1.47)**	1.18 (1.77)	1.53 (1.72)	1.12 (2.11)	1.96 (2.15)
p value	< 0.01	< 0.01	NS	< 0.01	NS	< 0.01
Working history						
No	2.66 (1.53)	2.02 (1.50)	1.18 (1.80)	1.59 (1.76)	1.10 (2.15)	2.12 (2.06)
Yes	2.89 (1.52)**	2.09 (1.49)	1.22 (1.74)	1.74 (1.80)*	1.21 (2.15)	2.22 (2.25)
p value	< 0.01	NS	NS	< 0.05	NS	NS
Income (US $/month)						
< 850	2.68 (1.52)	2.01 (1.50)^{a}	1.24 (1.81)^{b}	1.65 (1.77)^{b}	1.22 (2.23)^{b}	2.19 (2.07)^{b}
850–1699	2.78 (1.56)	2.17 (1.49)^{b}	1.08 (1.71)^{a}	1.44 (1.64)^{a}	1.02 (1.90)^{a}	1.96 (2.02)^{a,b}
≥ 1700	2.74 (1.52)	2.05 (1.47)^{a,b}	1.06 (1.71)^{a}	1.34 (1.70)^{a}	0.95 (2.08)^{a}	1.81 (2.07)^{a}
p value	NS	< 0.05	< 0.01	< 0.01	< 0.01	< 0.01
Rice consumption†						
< 50%	2.75 (1.54)	2.09 (1.51)**	1.12 (1.74)	1.55 (1.75)	1.01 (2.27)	2.04 (2.09)
> 50%	2.67 (1.52)	1.96 (1.47)	1.24 (1.82)**	1.66 (1.76)**	1.23 (2.04)**	2.22 (2.04)*
p value	NS	< 0.01	< 0.01	< 0.01	< 0.01	< 0.05

GM geometric mean, *GSD* geometric standard deviation, *NS* statistically nonsignificant

^{a,b,c,d}Duncan grouping

*$p < 0.05$, **$p < 0.01$

†Proportion of locally produced rice consumption to that of total rice consumption

respectively, which exceeded the biological exposure index (BEI) of American Conference of Governmental Industrial Hygienists (ACGIH), i.e., 5 μg/L or 5 μg/g creatinine, respectively (ACGIH 2015). No blood Pb levels greater than 25 μg/dL, the threshold for possible increased risk for adverse health effects, were observed (Schulz et al. 2007). However, 252 subjects had blood or urine Cd levels over the guideline levels. High NAG was observed in 16.9% of subjects (29/172), high ß$_2$-MG in 25.6% (44/172), and low eGFR in 14.4% (18/125) among participants in the subsequent study assessing kidney damage (Table 6).

Discussion

This cross-sectional study of the second phase health survey (2013−2017) was performed to monitor the exposure levels to Pb and Cd in 4500 inhabitants living near 104 abandoned metal mines in Korea. The geometric means of blood Pb (2.27 μg/dL), blood Cd (1.42 μg/L), and urine Cd (1.66 μg/g creatinine) in study subjects were lower than those from the 2008−2011 first phase health survey of 38 abandoned metal mines (2.87 μg/dL for blood Pb, 1.60 μg/L for blood Cd, Park et al. 2014; 2.19 μg/g

Table 4 Multiple regression to analyze the factors contributing to Pb or Cd levels in study subjects

Metals	Characteristics	Male β	Female β	Total β
Blood Pb	Sex	–	–	-0.206**
	Age	–	–	-0.001*
	Duration of residence	–	–	–
	Smoking	0.064**	–	0.061**
	Alcoholic drinking	0.108**	0.089**	0.092**
	Working history	0.069**	–	0.062**
	Rice consumption	–	-0.067**	-0.053**
	Income	–	–	–
Blood Cd	Sex	–	–	0.403**
	Age	0.004**	0.003*	0.003**
	Duration of residence	0.002**	0.003**	0.003**
	Smoking	0.185**	0.121*	0.179**
	Alcoholic drinking	–	–	–
	Working history	–	–	–
	Rice consumption	0.064*	0.056*	0.060**
	Income	-0.049*	-0.048*	-0.047**
Urine Cd	Sex	–	–	0.686**
	Age	0.016**	0.009**	0.012**
	Duration of residence	–	0.002*	0.002**
	Smoking	0.121*	–	–
	Alcoholic drinking	–	-0.097*	–
	Working history	–	–	–
	Rice consumption	0.177**	0.077**	0.119**
	Income	–	–	–

β: regression coefficient; $*p < 0.05$; $**p < 0.01$

Table 5 Spearman's rank correlation coefficients among metals in study subjects

	Blood Pb	Blood Cd	Urine Cd
Blood Pb	1		
Blood Cd	-0.0431**	1	
Urine Cd	-0.1708**	0.5200**	1

$**p < 0.01$

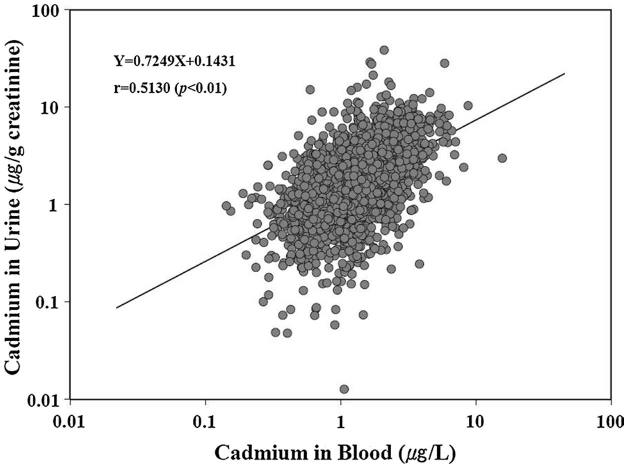

Fig. 2 Relationship between Cd levels in blood and urine

creatinine for urine Cd, unpublished data). Previously, the priority of the health surveys of abandoned metal mine inhabitants was ranked by the Ministry of Environment in 2007 based on the levels of environmental contaminants and potential for human exposure and included inhabitants' interest in environmental pollution. The top 38 regions were surveyed in the first phase, and, subsequently, 104 areas were surveyed in the second phase. According to the present study, human exposure to metals was still higher in abandoned metal mine area inhabitants than in the general population, as shown in the Korea National Environmental Health Survey (KoNEHS, 1.60 μg/dL for blood Pb, 0.43 μg/g creatinine for urine Cd; Statistics Korea 2017) and the Korea National Health and Nutrition Examination Survey (KNHANES, 1.42 μg/dL for blood Pb, 0.71 μg/L for blood Cd; Korea Centers for Disease Control and Prevention [KCDC] 2017). These findings indicate that abandoned metal mine area inhabitants are currently much more exposed to Pb and Cd compared with general population.

In the present study, blood Pb was higher in males than in females. It also was higher in smokers and alcohol drinkers than in nonsmokers and nondrinkers, which corresponds to the contributing factors to blood Pb levels in the general population (Eom et al. 2018; Son et al. 2019). Blood Pb was higher in males who had a work history in metal mines; however, it was not affected by consumption of locally produced rice or by duration of residence in males or in females. Cd levels in blood or urine were higher in females than in males and higher in smokers and in subjects with lower incomes, findings which concur with results from previous studies of the contributing factors to Cd in blood or urine in the general population (McKelvey et al. 2007; Eom et al. 2017, 2018). Cd levels in blood and urine were not associated with a work history in metal mines; however, they were higher in both male and female subjects who consumed locally produced rice. In addition, Cd levels in blood and urine increased in an age-dependent pattern until age 80 years and also by the duration of residence in the abandoned mine area. Furthermore, consumption of locally produced rice and duration of residence affected human exposure to Cd, which differed from Pb exposure in this study. These findings suggest that Cd is more associated with human exposure in abandoned mine areas than Pb, even though Pb and Cd concentrations in soil surrounding abandoned mines are higher than in noncontaminated areas in Korea (Jung 2008; Ji et al. 2013). This

Table 6 Proportions of high NAG, high β_2-MG, and low eGFR among participants in the following health effect study among high-Cd exposed subjects

Biomarkers	Criteria	High blood Cd (> 5 µg/L)	High urisne Cd (> 5 µg/g creatinine)	High Cd[a]
		80/4489 (1.8%)	185/2668 (6.9%)	252
NAG (unit/g creatinine)	> 11.5	12/64 (18.8%)	20/116 (17.2%)	29/172 (16.9%)
β_2-MG (µg/g creatinine)	> 300	25/64 (39.1%)	20/116 (17.2%)	44/172 (25.6%)
eGFR (mL/min/1.73 m^2)	< 60	16/55 (29.1%)	2/74 (2.7%)	18/125 (14.4%)

[a] Blood Cd > 5 µg/L or urine Cd > 5 µg/g creatinine

could be partially explained by the differences between Pb and Cd in terms of bioavailability and transfer factor from soil to plants (Liu et al. 2005; Cai et al. 2015). Namely, Cd is much more bioavailable and readily transferred from soil to plants than Pb is (Cai et al. 2015); therefore, Cd tends be strongly accumulated in plants, especially rice, that are grown in soils of formal mining areas contaminated with Pb and Cd (Liu et al., 2005). Eventually, people are exposed to Cd through the ingestion of harvested crops, mainly rice, from contaminated soils. Therefore, abandoned metal mine area inhabitants are exposed to more Cd than to Pb. Moreover, Cd has a relatively long biological half-life in the human body (Sugita and Tsuchiya 1995).

Furthermore, Cd concentrations in blood and urine increased in an age-dependent manner up to the 80-and-older age group, which differ from the trend observed in the general population; an age-dependent pattern for blood Pb also was observed in this study. In the general population, Cd in blood and urine usually increases until 50–60 years of age and then tends to decrease slightly or plateau (Lee et al. 2012; Sun et al. 2016; Eom et al. 2018). The findings of age-dependent increases in Cd levels in blood and urine in the subjects in this study are compatible with those in Japanese females (aged 40–79 years) in Cd-polluted areas; that is, blood and urine Cd levels demonstrated significant age-dependent increases in subjects from Cd-polluted area but were not associated with age in subjects from control area (Horiguchi et al. 2013). In this study, urine Cd was highly significantly associated with the recent Cd exposure index, i.e., blood Cd (Fig. 2). These findings indicate that abandoned mine area inhabitants are still exposed to Cd. Several previous studies have reported positive relationships between Cd and Pb, which are toxic and nonessential metals, in the general population ($r = 0.34$ for Cd and Pb in blood, Navas-Acien et al. 2009; $r = 0.498$ for Cd and Pb in blood, Eom et al. 2018). In contrast with those in the general population, Cd levels in blood and urine of subjects in this study were negatively correlated with blood Pb. These results could be ascribed to the above-mentioned differences between Cd and Pb in factors contributing to human exposure, such as bioavailability, transfer factor from soil to plants, age-dependent increases, consumption of locally produced rice, and duration of residence in the abandoned mine areas. Our findings suggest that inhabitants living near abandoned metal mines may be continuously exposed to Cd and sustainable rather than Pb even though mining activities ended several decades ago in Korea.

In the present study, no blood Pb levels > 25 µg/dL were observed, which is considered to be the threshold for possible increased risk for adverse health effects (Schulz et al. 2007). Cd levels in blood and urine also were significantly lower than BEI (5 µg/L and 5 µg/g creatinine, respectively, ACGIH 2015). However, the proportions of subjects with blood Cd and urine Cd levels exceeding BEI were 1.8% (80/4489) and 6.9% (185/2668), respectively. It is well known through several epidemiologic studies that chronic Cd exposure may induce tubular and/or glomerular damage to the kidneys of Cd-contaminated or non-contaminated area inhabitants (Tsuchiya 1969; Suwazono et al. 2000; Åkesson et al. 2005; Huang et al. 2013; Eom et al. 2017; Mezynska and Brzóska, 2018). Unfortunately, we were able to obtain biomarkers of adverse renal effects only from participants in the subsequent study among 252 subjects whose blood Cd level exceeded 5 µg/L or urine Cd level exceeded 5 µg/g creatinine, as the present study was designed primarily to monitor Pb and Cd exposure levels. Therefore, it was extremely difficult to evaluate the degree of the effects of Cd on renal damage or to provide acceptable Cd levels for health risk prevention in abandoned mine area inhabitants compared with those in the general population. However, our data, such as high NAG at 16.9%, high ß$_2$-MG at 25.6%, and low eGFR at 14.4% among the subsequent study participants, could suggest that kidney damage may be more commonly induced in abandoned metal mine area inhabitants than in the general population (Navas-Acien et al. 2009; Thomas et al. 2009; Hwangbo et al. 2011; Eom et al. 2017). To assess the potential health risk from Cd in abandoned mine area inhabitants, comparison with our previous epidemiologic study of the general population in non-Cd-polluted areas was made (Eom et al. 2017). Accordingly, we observed that urine Cd was positively correlated with NAG and ß$_2$-MG and negatively correlated with eGFR, high NAG at 4.2%, high ß$_2$-MG at 3.1%, and low eGFR at 2.0%; the 95th percentile of urine Cd concentration was 2.95 µg/g creatinine in the general population (Eom et al. 2017). Of the study subjects, 22.5% (601/2668) were greater than 2.95 μg/g creatinine in urine Cd and were expected to have a higher potential kidney risk than the general population. This comparison of urine Cd levels between abandoned mine area inhabitants and the general population suggests that people living near abandoned mines have a greater potential health risk, such as for kidney damage, by Cd exposure compared with that of the general population in nonpolluted areas. A previous epidemiologic study in Cd-contaminated areas of Japan also suggested that increased $ß_2$-MG at levels of > 300 μg/g creatinine by Cd exposure may contribute to increased mortality (Nakagawa et al. 1993).

This study demonstrated that the concentrations of blood Pb, blood Cd, and urine Cd were higher in abandoned metal mine area inhabitants than in the general population of Korea. Consumption of locally produced rice, duration of residence, and age influenced the levels of Cd, but not of Pb, in blood and urine in abandoned mine area inhabitants, and Cd in blood and urine negatively correlated with blood Pb. In addition, some inhabitants exceeded the thresholds of blood Cd or urine Cd. Taken together, abandoned metal mines can lead to continuous human exposure to Cd, but not to Pb, through crops grown in contaminated soils, which may eventually lead to adverse health effects such as kidney damage. Because abandoned mine areas can pose a great potential health risk, it is necessary to maintain continuous bio-monitoring and risk assessment and to prepare measures to reduce environmental health risks through environmental pollution control and health promotion.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest.

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