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Effects of Environmental Cadmium Exposure on the Liver in Korean Adults: Cross-Sectional and Longitudinal Studies

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Abstract

Cadmium (Cd) is a ubiquitous environmental pollutant with an exceptionally long biological half-life. The liver is a major organ for Cd metabolism, but the toxicity of Cd is unclear. This study sought to determine whether blood Cd (BCd) level (representing recent exposure [months] to Cd) was associated with liver function in Korean adults, both cross-sectionally and longitudinally. The baseline cross-sectional study involved 2,086 adults (male: 908, female: 1,178) in 2010 – 2011, and 503 of them (male: 207, female: 296) were followed up in 2014 – 2015. BCd was measured by graphite-furnace atomic absorption spectrometry, and liver function indices (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyltransferase [GGT]) were determined. Liver damage was defined as an abnormal elevation of more than one liver function index. The geometric mean of BCd (1.07 μg/L) was higher in females than in males (1.16 vs. 0.96 μg/L). Liver function indices increased significantly in a dose-dependent manner according to the BCd levels, except for ALT in males, and were higher in males than in females. BCd level was also associated with the risk of liver damage in both sexes. No significant changes in BCd were observed between baseline and follow-up. The liver function indices in 2014 – 2015 were comparable to those in 2010 – 2011 in males, while ALT and GGT were significantly increased in 2014 – 2015 compared to 2010 – 2011 in females with relatively high BCd. These findings suggest that even a low level of environmental Cd exposure, short- and long-term, may affect liver function, and females appear more susceptible than males.

Cadmium (Cd) is a non-essential element that tends to accumulate in the human body, causing toxicity and carcinogenicity (IARC 1993; ATSDR 2012). Cd may also cause various non-carcinogenic diseases, including lung, kidney, bone, liver, cardiovascular system, and reproductive system, as well as increased mortality (Godt et al. 2006; Menke et al. 2009; Tinkov et al. 2018).

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Cd is a major environmental pollutant emitted from natural/geogenic sources as well as anthropogenic sources mainly related to the activities of mining and industries, such as smelting, refining, electroplating, battery production, fertilizers, color pigments, and stabilizers (ATSDR 2012; Genchi et al. 2020). It is well known that Cd is persistent in the environment, is not biodegradable, and has an exceptionally long half-life (25 – 30 years) in the body (ATSDR 2012). The absorbed Cd into the body is deposited in the liver initially, then transported to the kidneys, and eventually accumulated there. In our previous estimation of the reference Cd levels in the general Korean population, the mean concentration of Cd in the renal cortex was approximately nine times higher than that in the liver, and the difference between the Cd concentration in the renal cortex and liver increased with biological age up to the 50 s, and plateaued after that, differences were not large prior to age 10 (Park et al. 2000). This finding supported that Cd preferentially accumulates in the kidney and may cause kidney damage due to its long biological half-life (Järup et al. 1998; Bernard 2004). That

long-term exposure to Cd can cause kidney damage was first observed in 1912 and identified in 1968 as "*Itai-Itai*" ("ouch-ouch") disease by the Japanese Ministry of Health and Welfare (Tsuchiya 1969). Since then, Cd-induced kidney damage has also been reported in the general population under the environmental exposure of low-dose Cd and in workers with occupational exposure to Cd (Järup et al. 1998; Järup and Åkesson 2009; Eom et al. 2017).

The liver is a vital organ, the major site of xenobiotic metabolism, and the second main organ of Cd accumulation in the body (Arroyo et al. 2012). Liver Cd represents recent exposure (months), including chronic exposure, while kidney Cd is more indicative of long-term exposure. Although urinary Cd and blood Cd (BCd) are useful indicators of body Cd exposure, urinary Cd may more closely reflect chronic exposure, such as total body burden, and BCd may reflect more recent exposure (Godt et al. 2006; Arroyo et al. 2012).

Previously, liver damage by Cd was reported in experimental animal studies, both acute and chronic (Dudley et al. 1984, 1985; Habeebu et al. 2000). However, liver toxicity in Cd-exposed workers has been rarely reported (Attia et al. 2009; ATSDR 2012; Tomei et al. 2013), and no evidence for Cd-induced liver damage was found in the general Japanese population (Ikeda et al. 1997, 2000). During the last decade, several epidemiology studies have reported liver damage due to environmental exposure to low levels of Cd in the general population (Hyder et al. 2013; Kang et al. 2013; Chung et al. 2020; Hong et al. 2021), representing a grave concern to human health. However, these previous epidemiology studies of the association between Cd exposure and liver damage were limited to cross-sectional studies. Therefore, further studies are required to substantiate the association between environmental Cd exposure and liver damage in the general population and to evaluate whether current Cd exposure levels may adversely affect liver function in the short- and long-term.

The body burden of Cd in Koreans is higher than that in several Western countries, including the US (Becker et al. 2002; Akerstrom et al. 2013; CDC 2015; Health Canada 2015). Recently, non-alcoholic fatty liver disease (NAFLD) has been increasing worldwide, including in Korea, and liver disease is one of the major causes of death in the Korean population, ranking as the eighth leading cause of death (Lee et al. 2019; Statistics Korea 2021). Therefore, there is an urgent need to evaluate the adverse effects of environmental low-level Cd exposure on liver function in order to take a stand regarding policies in protecting and promoting human health by reducing Cd exposure in the general population.

In this study, we investigated the relation between BCd and liver function using hepatic enzyme activities (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ- glutamyltransferase [GGT]) in the general Korean population. Furthermore, we evaluated whether the levels of BCd were predictive of the changes in liver function after 4 – 5 years.

Materials and Methods

Study Subjects

This study used the data from a cross-sectional (baseline) study in 2010 – 2011 and a follow-up study 4 – 5 years later, in 2014 – 2015. The baseline data, drawn from a representative sample of Korean adults (Lim et al. 2015), included 2086 healthy adults (male: 908, female: 1178) aged 19 years or over who had not been exposed to Cd occupationally. The study subjects were sampled nationwide from 102 different sampling sites by a stratified (sex and age) probability method. The number of study subjects in each site was allocated by the square root proportional method based on the population size of each relevant district. In the follow-up study, 4 – 5 years later, 503 subjects (male: 207, female: 296) among the baseline study subjects voluntarily participated in blood sampling. A personal interview was performed using a structured questionnaire by well-trained personnel to collect demographic information, such as age, gender, smoking, alcohol drinking, education level, and occupational history. Smoker was defined as smoking at least 100 cigarettes during their lifetime, and non-drinker was defined as consuming no alcohol during 1 month prior to the interview. Height, weight, and blood pressure were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI over 25 kg/m^2 was defined as obese or overweight, specifically for Koreans (Seo et al. 2019). The study protocol was approved by the Chung-Ang University Ethical Committee for Medical Research and Other Studies Involving Human Subjects in 2010 – 2011 (CAUEC 2010-06-01) and the Institutional Review Board of Dankook University Hospital in 2014 – 2015 (DKUH 2014-02-016). Written consent was obtained from every participant in both studies.

Blood Sampling

Blood sampling was performed by experienced nurses. Whole blood for BCd determination was sampled with a heparin-treated vacutainer tube. The serum was separated by centrifugation at 1000 X g for 10 min from whole blood collected in a serum separating tube (SST) of polystyrene. Whole blood was stored at – 80 °C for Cd analysis.

Analysis of Cd in Whole Blood

The concentration of Cd in whole blood was determined using two different atomic absorption spectrometers

equipped with graphite-furnace (GF-AAS; Thermo, Inc., Cambridge, UK; AAnalyst 600, Perkin-Elmer, Norwalk, CT) in 2010 – 2011 and 2014 – 2015, respectively. In brief, whole blood was diluted using 0.2% Triton X-100 with 1% nitric acid and 0.2% diammonium hydrogen phosphate and then mixed vigorously. A 15 µL aliquot of the diluted sample was injected into a graphite tube, following three steps of dry, ash, and atomization. The analysis of Cd in whole blood was validated in terms of linearity of calibration curve, accuracy and precision using standard reference material (SRM, Bio-Rad Lyphochek Whole Blood Metals Control, Irvine, CA) with an international quality control program (EQUAS, Germany). The calibration curve was linear ($r = 0.999$), recovery and coefficient of variation of SRM was 98.7 and 2.76%, respectively. The limit of detection for Cd in blood was 0.1 µg/L. As mentioned above, the analytical instrument used in the follow-up study differed from that used in the baseline study. The consistency in analysis of BCd according to measuring period, 2010 – 2011 or 2014 – 2015, was evaluated by repeated measurements of the Cd concentration for 30 samples of whole blood sampled in 2010 – 2011. The difference from the values at baseline was not significant and well-correlated with the re-measured values ($r = 0.933$). BCd below the detection limit was assigned the value of the detection limit divided by the square root of two.

Measurement of AST, ALT, and GGT

Liver function was evaluated by measuring the activities of AST, ALT, and GGT in the serum using enzymatic methods on a chemistry autoanalyzer (Roche-Hitachi Cobas 8000 c702, Roche Diagnostics, Germany): ASTL reagent (Roche, Germany) to measure AST and ALT levels, and GGT-2 reagent (Roche, Germany) to measure GGT activity. The criteria for abnormal liver function included AST (> 40 IU/L), ALT (> 40 IU/L), and GGT (> 73 IU/L for males and > 48 IU/L for females). Liver damage was defined as meeting more than one criterion for abnormal liver function (AST, ALT, and GGT).

Statistical Analyses

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC). The concentration of BCd was log-transformed because the data were log-normally distributed rather than normally distributed. BCd was presented as geometric mean (GM) and geometric standard deviation (GSD), and age, height, weight, BMI, and liver function indices were expressed as arithmetic mean (AM) and standard deviation (SD). Means were compared by performing the Student *t*-test or analysis of variance (ANOVA), followed by Duncan's multiple comparison test. The levels of BCd were categorized into tertiles (lowest, intermediate, and highest) based on the baseline study in 2010 – 2011. The generalized linear model (GLM) was performed to compare the adjusted means of liver function indices according to the BCd levels after controlling for various potential confounding factors, such as age, smoking, alcohol drinking, education level, and BMI. The association of BCd levels with liver damage was evaluated by multivariate logistic regression analyses, and the risk of liver damage was presented with the odds ratio (OR) and the 95% confidence interval (CI) according to the BCd levels. In addition, the differences in BCd and liver function indices between the 2010 – 2011 and 2014 – 2015 studies were analyzed by a paired *t*-test in the repeated measured individuals. The level of statistical significance was set at $p < 0.05$.

Results

Baseline Study

The mean age of the study subjects in the baseline study (2010 – 2011) was 45.7 years and was not significantly different between males and females. Height, weight, and BMI were higher in males than in females. The liver function indices (AST, ALT, and GGT) were significantly higher in males than in females. The GM concentration of BCd was 1.07 µg/L in the total study subjects and was significantly higher in females (1.16 µg/L) than in males (0.96 µg/L). The AM concentration of BCd was 1.24 µg/L (1.12 µg/L in males and 1.34 µg/L in females), and the 95th percentile of BCd was 2.58 µg/L (2.35 µg/L in males and 2.69 µg/L in females, Table 1). Therefore, further analyses were performed according to sex.

The level of BCd was significantly increased according to the age group in both males and females. BCd was significantly increased by smoking habit in males, being highest in current smokers, followed by ex-smokers and non-smokers. No statistical significance was observed for smoking habits in females. The level of BCd was higher in drinkers than non-drinkers in males, while the opposite pattern was observed in females. The highest BCd was observed in the less educated males and females (Table 2). AST, ALT, and GGT increased by age group and generally increased inversely with the education level, except for ALT in males. GGT was higher in smokers (both males and females) and higher in drinkers in males only. The effects of smoking or alcohol drinking on AST and ALT were not consistent between males and females. The levels of liver function indices (ALT, AST, and GGT) and BCd were significantly higher in obese or overweight people (BMI ≥ 25 kg/m^2) than in people with a BMI below 25 kg/m^2 (Table 2).

The BCd level was divided into tertiles in males (Q1, low 1/3, < 0.79; Q2, intermediate 1/3, 0.79 – 1.23; Q3,

Table 1 Means of age, height, weight, BMI, liver function indices, and BCd in the baseline study (2010 – 11)

Variables		Male	Female	Total	*p*-value
N		908	1,178	2,086	
Age (years)		45.6 ± 15.0	45.8 ± 14.1	45.7 ± 14.5	NS
Height (cm)		169.7 ± 6.6	156.8 ± 5.9	162.4 ± 8.9	< 0.01
Weight (kg)		70.6 ± 10.9	58.3 ± 8.9	63.7 ± 11.6	< 0.01
BMI (kg/m^2)		24.5 ± 3.1	23.8 ± 3.5	24.1 ± 3.4	< 0.01
AST (IU/L)		24.4 ± 15.2	20.2 ± 9.5	22.0 ± 12.5	< 0.01
ALT (IU/L)		25.7 ± 17.7	17.7 ± 13.2	21.2 ± 15.8	< 0.01
GGT (IU/L)		50.0 ± 65.5	20.9 ± 24.8	33.5 ± 49.2	< 0.01
BCd (μg/L)	AM ± SD	1.12 ± 0.63	1.34 ± 0.72	1.24 ± 0.70	< 0.01
	GM (GSD)	0.96 (1.75)	1.16 (1.73)	1.07 (1.75)	< 0.01
	Range	0.13–4.79	0.07–5.72	0.07–5.72	
	95th percentile	2.35	2.69	2.58	

Abbreviations: BMI: body mass index, BCd: blood cadmium, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, AM: arithmetic mean, SD: standard deviation, GM: geometric mean, GSD: geometric standard deviation, NS: not significant

Table 2 Means of BCd (μg/L) and liver function indices (IU/L) by demographic characteristics of the participants in the baseline study (2010 – 11)

Variables	Male					Female				
	N	BCd	AST	ALT	GGT	*N*	BCd	AST	ALT	GGT
Age (years)										
< 29	173	0.59 (1.80)^a	21.7 ± 11.5^a	25.3 ± 25.0	27.7 ± 24.7^a	180	0.61 (1.76)^a	17.1 ± 6.1^a	14.2 ± 13.1^a	15.3 ± 16.4^a
30 – 49	344	1.02 (1.68)^b	24.0 ± 13.9^{ab}	27.3 ± 17.6	51.3 ± 51.1^b	489	1.19 (1.652^b	18.8 ± 8.7^b	16.6 ± 13.2^b	19.9 ± 23.3^b
> 50	391	1.14 (1.58)^c	25.9 ± 17.4^b	24.4 ± 13.2	58.7 ± 84.3^b	509	1.41 (1.52)^c	22.8 ± 10.5^c	20.1 ± 12.8^c	23.8 ± 28.1^c
p-value		< 0.01	< 0.01	NS	< 0.01		< 0.01	< 0.01	< 0.01	< 0.01
Smoking										
Non-smokers	239	0.66 (1.71)^a	23.5 ± 11.1	25.2 ± 21.6	40.6 ± 56.4^a	1022	1.15 (1.73)	20.3 ± 9.7	17.6 ± 13.0	20.3 ± 19.8^a
Ex-smokers	289	0.90 (1.58)^b	25.0 ± 11.6	26.3 ± 15.5	48.5 ± 51.9^{ab}	97	1.16 (1.68)	20.0 ± 7.7	17.8 ± 11.4	19.2 ± 15.6^a
Smokers	367	1.30 (1.62)^c	24.5 ± 19.6	25.3 ± 16.5	57.2 ± 79.1^b	56	1.24 (1.89)	19.6 ± 7.9	19.8 ± 18.9	33.4 ± 72.9^b
p-value		< 0.01	NS	NS	< 0.01		NS	NS	NS	< 0.01
Alcohol drinking										
Non-drinkers	108	0.84 (1.71)	22.9 ± 9.8	24.5 ± 15.2	31.5 ± 25.5	404	1.27 (1.61)	21.5 ± 11.1	19.3 ± 13.4	22.0 ± 29.0
Drinkers	795	0.98 (1.75)	24.6 ± 15.8	25.9 ± 18.0	52.5 ± 68.8	768	1.11 (1.79)	19.6 ± 8.5	16.9 ± 13.0	20.2 ± 22.2
p-value		< 0.01	NS	NS	< 0.01		< 0.01	< 0.01	< 0.01	NS
Education										
< High school	224	1.17 (1.63)^a	26.5 ± 22.0^a	24.3 ± 12.8	64.4 ± 102.9^a	404	1.42 (1.52)^a	22.6 ± 9.8^a	19.8 ± 12.0^a	23.7 ± 29.7^a
High school	281	1.05 (1.64)^b	24.9 ± 13.8^{ab}	26.1 ± 18.1	53.9 ± 53.8^a	428	1.25 (1.61)^b	19.6 ± 8.4^b	17.2 ± 11.9^b	20.5 ± 22.2^{ab}
> High school	402	0.81 (1.81)^c	22.8 ± 10.7^b	26.1 ± 19.6	39.2 ± 39.4^b	344	0.83 (1.85)^c	18.3 ± 9.8^b	16.0 ± 15.6^b	18.0 ± 21.1^b
p-value		< 0.01	< 0.05	NS	< 0.01		< 0.01	< 0.01	< 0.01	< 0.01
BMI										
< 25	528	0.93 (1.80)	22.8 ± 16.0	21.4 ± 13.1	44.2 ± 72.7	797	1.10 (1.77)	19.3 ± 8.1	15.7 ± 10.6	18.1 ± 17.3
≥ 25	380	1.01 (1.69)	26.6 ± 13.7	31.6 ± 21.1	58.1 ± 52.9	381	1.30 (1.62)	22.3 ± 11.5	21.9 ± 16.7	26.5 ± 35.2
p-value		< 0.05	< 0.01	< 0.01	< 0.01		< 0.01	< 0.01	< 0.01	< 0.01

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

Abbreviations: BMI: body mass index, BCd: blood cadmium, AST: aspartate aminotransferase, NS: not significant, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase

high 1/3, ≥ 1.23) and females (Q1, < 0.97; Q2, 0.97 – 1.48; Q3, ≥ 1.48), respectively, to analyze the associations between BCd and the liver function indices. AST and GGT were significantly increased in a dose-dependent manner in both males and females, respectively, according to the BCd levels. These statistical significances remained after adjustment for age or various confounding variables, such as age, smoking, alcohol drinking, education level, and BMI. ALT also significantly increased according to BCd in females but not males (Table 3). The proportion of liver damage was 23.0% (209/908) in males and 6.8% (80/1,178) in females and increased dose-dependently to 17.2, 20.1, and 31.7% in males and 3.1, 6.4, and 10.9% in females in the lowest, intermediate, and highest tertiles of BCd, respectively. The risk of liver damage was significantly higher by 2.23 and 3.89 times in the highest tertile of BCd compared to the lowest tertile of BCd in males and females, respectively. The significant risk of liver damage by BCd level remained after adjustment against the potential confounding variables, such as age, smoking, alcohol drinking, education level, and BMI (Table 4).

Follow-up Study

The levels of BCd and liver function indices of 503 study subjects who were followed up in 2014 – 2015 among 2,086 study subjects who participated in the baseline study in 2010 – 2011 are shown in Table 5. No significant changes in BCd were observed between the baseline and follow-up studies in both males and females, respectively. The levels of liver function indices were similar between the baseline and follow-up studies in males. In females, although AST was not different between both studies, significant increases in ALT and GGT were observed in 2014 – 2015 compared to 2010 – 2011. Longitudinal changes in liver function indices according to the BCd levels based on the 2010 – 2011 study are presented in Table 6. No significant changes in AST, ALT, and GGT according to the BCd level were observed between the 2010 – 2011 and 2014 – 2015 studies in males. In females, although ALT was not different between the 2010 – 2011 and 2014 – 2015 studies in the lowest tertile of BCd, it was significantly increased in 2014 – 2015 compared to 2010–2011 in the intermediate and highest tertiles of BCd in females. Additionally, GGT was significantly higher in 2014 – 2015 compared to 2010 – 2011 in the intermediate tertile of BCd in females. Namely, increases in some liver function indices were observed in females with relatively high BCd in the 2010 – 2011 study exposed to a low environmental level of Cd in the general population (Table 6).

Discussion

This study analyzed whether environmental low-level Cd exposure affects liver function. The GM concentration of Cd in whole blood was 1.07 μg/L in the general Korean adult population. The mean levels of the liver function indices were 22.0 IU/L in AST, 21.2 IU/L in ALT, and 33.5 IU/L in GGT. Although the levels of BCd and liver function indices were similar to the previous reports on the general

Table 3 Liver function indices according to the blood cadmium levels in the baseline study (2010 – 11)

		Male				Female			
		N	Crude	M1	M2	*N*	Crude	M1	M2
AST (IU/L)	Q1	302	22.7 ± 10.0^{a}	23.2^{a}	23.0^{a}	392	18.1 ± 5.8^{a}	19.3^{a}	19.4^{a}
	Q2	303	23.6 ± 10.0^{a}	23.5^{a}	23.4^{a}	393	20.2 ± 8.3^{b}	19.9^{a}	19.9^{a}
	Q3	303	26.9 ± 22.0^{b}	26.5^{b}	26.8^{b}	393	22.4 ± 12.6^{c}	21.5^{b}	21.3^{b}
	p-trend		< 0.01	< 0.01	< 0.01		< 0.01	< 0.01	< 0.01
ALT (IU/L)	Q1	302	25.2 ± 19.7	24.7	24.3	392	15.3 ± 9.3^{a}	16.4^{a}	16.6^{a}
	Q2	303	26.0 ± 17.3	26.2	25.8	393	17.8 ± 14.0^{b}	17.5^{a}	17.5^{ab}
	Q3	303	25.8 ± 15.7	26.1	26.7	393	20.1 ± 15.1^{c}	19.3^{b}	18.9^{b}
	p-trend		NS	NS	NS		< 0.01	< 0.01	< 0.05
GGT (IU/L)	Q1	302	35.6 ± 35.8^{a}	38.1^{a}	40.9^{a}	392	17.3 ± 10.8^{a}	18.5^{a}	19.0^{a}
	Q2	303	47.4 ± 56.7^{b}	46.6^{a}	46.7^{a}	393	20.2 ± 25.1^{a}	19.9^{a}	20.0^{ab}
	Q3	303	67.0 ± 88.8^{c}	65.3^{b}	62.4^{b}	393	25.0 ± 32.8^{b}	24.1^{b}	23.0^{b}
	p-trend		< 0.01	< 0.01	< 0.01		< 0.01	< 0.01	< 0.05

*M1: age-adjusted, M2: age-, smoking-, alcoholic drinking-, education-, and BMI-adjusted. Blood cadmium criteria: Q1 (< 0.79), Q2 (0.79 – 1.23), and Q3 (≥ 1.23) in males, Q1 (< 0.97), Q2 (0.97 – 1.48), and Q3 (≥ 1.48) in females

[a, b, c] Duncan grouping

Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, NS: not significant, M1: model 1, M2: model 2, BMI, body mass index

Table 4 Liver damage according to the blood cadmium levels in the baseline study (2010 – 11)

Liver damage		Male		Female	
		N (%)	OR (95% CI)	*N* (%)	OR (95% CI)
Crude	Q1	52 (17.2)	1	12 (3.1)	1
	Q2	61 (20.1)	1.21 (0.80, 1.83)	25 (6.4)	2.15 (1.07, 4.34)
	Q3	96 (31.7)	2.23 (1.52, 3.28)	43 (10.9)	3.89 (2.02, 7.50)
	p-trend		< 0.01		< 0.01
Age-adjusted	Q1		1		1
	Q2		1.19 (0.78, 1.81)		1.93 (0.93, 3.99)
	Q3		2.18 (1.46, 3.26)		3.35 (1.65, 6.78)
	p-trend		< 0.01		< 0.01
Multivariate-adjusted	Q1		1		1
	Q2		1.18 (0.74, 1.87)		1.90 (0.90, 4.03)
	Q3		2.26 (1.38, 3.72)		2.93 (1.40, 6.12)
	p-trend		< 0.01		< 0.01
	Total	209 (23.0%)		80 (6.8%)	

*Multivariate-adjusted factors, including age, smoking, alcoholic drinking, education, and BMI

Blood cadmium criteria: Q1 (< 0.79), Q2 (0.79 – 1.23), Q3 (≥ 1.23) in males, Q1 (< 0.97), Q2 (0.97 – 1.48), Q3 (≥ 1.48) in females. Liver dysfunction criteria included AST (> 40 IU/L), ALT (> 40 IU/L), and GGT (> 73 IU/L for males and > 48 IU/L for females). Liver damage was defined as the presence of more than one of the liver dysfunction criteria

Abbreviations: OR; odds ratio, CI; confidence interval

Table 5 Means of BCd and liver function indices in the follow-up study (2014 – 15)

	Male (*n* = 207)			Female (*n* = 296)		
	2010–2011	2014–2015	*p*-value	2010–2011	2014–2015	*p*-value
Blood Cd (μg/L)	0.96 (1.69)	0.92 (1.70)	NS	1.18 (1.71)	1.13 (1.70)	NS
AST (IU/L)	25.3 ± 15.6	25.0 ± 15.1	NS	21.1 ± 10.3	19.7 ± 16.6	NS
ALT (IU/L)	25.9 ± 16.0	24.5 ± 12.7	NS	18.2 ± 13.8	21.2 ± 9.1	< 0.01
GGT (IU/L)	49.3 ± 52.1	48.3 ± 59.8	NS	20.1 ± 14.7	21.9 ± 16.5	< 0.05

*Difference between years 2010 – 11 and 2014 – 15 was tested by paired *t*-test

Abbreviations: BCd: blood cadmium, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, NS: not significant

Table 6 Longitudinal changes in liver function indices according to the blood cadmium levels in the baseline study (2010 – 11)

		Male (*n* = 207)				Female (*n* = 296)			
		N	2010 – 11	2014–15	*p*-value	*N*	2010 – 11	2014 – 15	*p*-value
AST (IU/L)	Q1	70	25.0 ± 12.7	25.0 ± 14.8	NS	92	20.1 ± 8.7	17.4 ± 13.0	< 0.05
	Q2	73	23.3 ± 10.4	24.7 ± 15.6	NS	107	20.3 ± 6.8	21.1 ± 20.6	NS
	Q3	64	28.1 ± 22.0	25.5 ± 15.1	NS	97	22.8 ± 14.1	20.5 ± 14.5	NS
ALT (IU/L)	Q1	70	26.5 ± 18.6	22.8 ± 8.3	NS	92	17.6 ± 13.0	19.4 ± 7.3	NS
	Q2	73	24.5 ± 14.8	23.9 ± 12.9	NS	107	17.6 ± 11.4	21.5 ± 9.9	< 0.01
	Q3	64	26.8 ± 14.3	27.0 ± 15.9	NS	97	19.4 ± 16.7	22.6 ± 9.6	< 0.01
GGT (IU/L)	Q1	70	37.9 ± 45.0	32.8 ± 22.1	NS	92	19.2 ± 14.1	21.2 ± 17.0	NS
	Q2	73	48.6 ± 58.9	52.1 ± 75.0	NS	107	18.0 ± 11.0	20.8 ± 15.9	< 0.05
	Q3	64	62.5 ± 48.6	60.8 ± 65.3	NS	97	23.3 ± 18.1	23.8 ± 16.7	NS

*Difference between years 2010 – 11 and 2014 – 15 was tested by paired *t*-test

Blood cadmium criteria: Q1 (< 0.79), Q2 (0.79 – 1.23), and Q3 (≥ 1.23) in males, Q1 (< 0.97), Q2 (0.97 – 1.48), and Q3 (≥ 1.48) in females

Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, NS: not significant

population of Korea (Kang et al. 2013; Park et al. 2021), the BCd from this study is still higher than those in the US and Western countries (Becker et al. 2002; Akerstrom et al. 2013; CDC 2015; Health Canada 2015), but it is similar or low compared to other Asian countries (Kurihara et al. 2004; Nie et al. 2016). One possible explanation for the higher level of BCd in Koreans, including other Asian populations, compared to Western populations could be their staple food, rice. Cd tends to accumulate more than other toxic metals in plants, especially rice, because of its relatively high bioavailability, and it can be readily transferred from soil to plants because of its higher mobility compared to other non-essential heavy metals, such as lead and mercury (Satarug et al. 2003; Liu et al. 2005; Cai et al. 2015; Moon et al. 2021). The main exposure source of Cd in the general population is the diet. In our previous study, the daily Cd intake from food in Koreans was estimated at 7.07 µg/day, of which approximately 33% came from grains, followed by seafood (29%), vegetables (20%) and others (Huang et al. 2013). However, the highest concentration of BCd was 5.72 µg/L, and only 3 among 2,086 study subjects had a BCd over 5 µg/L, the biological exposure index proposed by the American Conference of Governmental Industrial Hygienists (ACGIH 2014). This finding indicates that the study subjects had been exposed to low environmental levels of Cd.

In the study subjects, the BCd concentrations and liver function indices generally tended to increase with age, lower education level, and obesity in both males and females. These findings are concurrent with the results of previous studies. Age is a significant contributing factor to the liver enzyme levels and the body Cd level (Ikeda et al. 1997; Kang et al. 2013). Obesity (i.e., increased BMI) is closely linked to metabolic liver dysfunction and its progression to fatty liver (Kojima et al. 2003; Danielsson et al. 2014). In addition, individual lifestyles, such as smoking and alcohol drinking, may also contribute to increased Cd exposure, impaired liver function, or both. Though we have not measured Cd contents in cigarette and alcohol in this study, cigarette smoking is a well-known major source of environmental exposure to Cd equivalent to 0.5 – 1 µg/cigarette (Satarug and Moore 2004). Blood Cd was higher in drinkers than in non-drinkers (Martins et al. 2020) also was significantly higher in relation to alcohol consumption in male smokers (Choi et al. 2020). In addition, excessive smoking and alcohol drinking affect liver function (Klatsky and Armstrong 1992; El-Zayadi 2006; Danielsson et al. 2014; Åberg et al. 2020). Therefore, individual lifestyles including smoking and alcohol drinking could contribute to the potential health issues by Cd exposure. In the current study, the BCd concentrations were increased by smoking habits and alcohol drinking in males but not in females, and no significant effects of smoking and alcohol drinking on AST and ALT were observed in both sexes. However, GGT was affected by smoking in both sexes and alcohol drinking in males only. Some inconsistent effects of smoking and alcohol drinking on liver function compared to previous studies could be ascertained and partially explained by several factors, such as the limited number of smokers among females and the relatively broad definition of alcohol drinkers. Conversely, some epidemiology studies have reported that smoking and alcohol drinking were not associated with hepatic steatosis (Chung et al. 2020), and the effects of smoking or alcohol drinking were inconsistent according to liver function parameters (Danielsson et al. 2014; Hong et al. 2021). However, smoking and alcohol drinking were considered as potential risk factors that could affect liver function in the further analysis of this study, along with age, education level, and obesity.

Cd-induced liver damage has been demonstrated, both after acute and chronic exposure, in several experimental animal studies (Dudley et al. 1984, 1985; Habeebu et al. 2000). The mechanisms of liver damage by Cd, in vitro and in vivo studies, are suggested to involve direct and indirect oxidative stress processes, such as increases in the production of reactive oxygen species, decreases in antioxidative enzymes and non-enzymatic antioxidants, inflammation by activation of Kupffer cells and increased production of interleukin-1-beta (IL-1β), interleukin-8 (IL-8), and C-reactive protein (CRP), and abnormal lipid metabolism by stimulation of c-Jun N-terminal kinase activation (Rikans and Yamano 2000; Go et al. 2015; Mezynska and Brzóska 2018; Werder et al. 2020; Wang et al. 2021) as well as Cd in the liver exceeding the hepatic metallothionein available to sequester Cd (Habeebu et al. 2000). A few studies have reported the effect of Cd exposure on liver damage in industrial workers, but the results did not support that Cd was a causative agent of liver injury in occupationally Cd-exposed workers (Attia et al. 2009; Tomei et al. 2013). Furthermore, Ikeda et al. (1997, 2000) reported that environmental Cd exposure did not affect liver function among general Japanese females, despite relatively high Cd levels in the blood (GM of 2.17 and 1.76 µg/L) and urine (1.98 and 3.94 µg/g of creatinine). Similarly, no association between blood BCd and ALT elevation was observed in the US adult general population (Cave et al. 2010). These findings might have downplayed the concerns of liver function damage induced by low-dose, chronic environmental exposure to Cd in the general population.

Evidence suggests that the BCd level accepted as safe for the general population (5 µg/L) may be too high (ACGIH 2014). An association between urinary Cd and liver dysfunction has been reported in the US based on the National Health and Nutrition Examination Survey (NHANES) in 1988 – 1994 (Hyder et al. 2013) and the 1999 – 2015 NHANES (Hong et al. 2021). Hyder et al. (2013) indicated an increased risk of hepatic necroinflammation in the highest quartile of urinary Cd ($\geq$0.65 µg/g of creatinine for

males, ≥ 0.83 μg/g of creatinine for females) compared to the lower quartiles in both males (OR 2.21, 95% CI 1.64 – 3.00) and females (OR 1.26, 95% CI 1.01 – 1.57). Furthermore, Hong et al. (2021) presented that liver function parameters, including ALT, AST, and GGT, were positively associated with the urinary Cd level in study subjects with a GM of 0.27 μg/g of creatinine. In both of these previous studies, the levels of urinary Cd were much lower than those in the Korean general population, with a GM of 0.82 and 1.36 μg/g of creatinine in males and females, respectively (Eom et al. 2017). Based on data from the Korea National Health and Nutrition Examination Survey (KNHANES) in 2008 – 2009, the level of BCd under environmental exposure was associated with an elevation of the serum liver enzymes AST, ALT, and alkaline phosphatase (ALP) in the Korean adult population (Kang et al. 2013). Subsequent studies indicated that BCd was associated with an increased risk of hepatic fibrosis in females in 2016 and 2017 (Chung et al. 2020) and with the risk of NAFLD in 2008 – 2013, 2016, and 2017 (Park et al. 2021) based on KNHANES. Those studies concerned environmental exposure to Cd in the general population, and the levels of BCd were similar to those in this study population (GM, 1.07 μg/L), which was performed independently from KNHANES.

In the present study, the serum activity of liver enzymes increased dose-dependently according to the BCd level in both males and females, except for ALT activity, which increased dose-dependently according to the BCd level in females only. However, the risk of liver damage was significantly higher in the highest tertile of BCd (OR 2.23, 95% CI 1.52 – 3.28) compared to the lowest tertile in males, while it was significantly higher in both the intermediate tertile (OR 2.15, 95% CI 1.07 – 4.34) and the highest tertile of BCd (OR 3.89, 95% CI 2.02 – 7.50) compared to the lowest tertile in females. The significantly increased risks of liver damage in the highest tertile of BCd compared to the lowest tertile of BCd (≥ 1.23 vs. < 0.79 for males; ≥ 1.48 vs. < 0.97 for females) remained in both males and females (risk increased by 2.26- and 2.93-fold, respectively) after controlling for potential confounding variables, such as age, smoking, alcohol drinking, education level, and BMI as well as age. The cutoffs for the highest tertile of BCd in this study could not be compared directly with the previous mean BCd (1.98 ± 0.70 μg/L) in the highest quartile of BCd, which was significantly ($p < 0.0001$) associated with elevated liver enzyme levels (Kang et al. 2013), but the values were comparable with the cutoffs for BCd of 0.96 and 1.41 μg/L, for suspected NAFLD and hepatic steatosis, respectively, suggested by Park et al. (2021). Meanwhile, the suggested Cd levels associated with abnormal liver function, including those in the current study, are much lower than the recommended biological exposure index (ACGIH 2014). Furthermore, the BCd was not different between the baseline (2010 – 2011) and follow-up (2014 – 2015) studies in the subjects who participated in both studies (503/2086), but a statistically significant elevation of ALT or GGT or both were observed in the tertiles of BCd in females, except for the lowest tertile. These findings suggest that a relatively high BCd exceeding 0.97 μg/L, even after low environmental exposure to Cd, may affect liver function in the short- and long-term only in females.

The susceptibility of human health to Cd according to sex varies among researchers. Namely, *Itai-Itai* disease was prevalent in females, especially those over the age of 40 and those who had experienced multiple deliveries (Tsuchiya 1969). In Korean adults, females were more susceptible to environmental Cd exposure (Huang et al. 2013), and an association between BCd and hepatic fibrosis was reported in females only (Chung et al. 2020). The mortality risk was more closely associated with an increase in urinary β_2-microglobulin in females than in males in a Cd-polluted area of Japan (Nishijo et al. 2004). By contrast, urinary Cd was associated with an increased risk of all-cause, cancer, and cardiovascular disease mortality among male US adults but not among female US adults (Menke et al. 2009), and environmental Cd exposure was more associated with liver dysfunction in males than in females among US adults (Hyder et al. 2013). Susceptibility to Cd by sex might be explained partially by a relatively lower level of essential minerals, such as iron and zinc, activation of receptor-mediated calcium channels by progesterone, and endocrine-like effects in the body as endocrine disruptor (Åkesson et al. 2002; Baker et al. 2003; Ryu et al. 2004; Vahter et al. 2007; Strumylaite et al. 2019; White et al. 2019; Wei and Zhu 2020). However, the mechanism of action is still controversial yet. This study has several limitations. In particular, the interval between the baseline and follow-up studies was not enough to respond to additional Cd exposure, the proportion of baseline study subjects who participated in the follow-up study was relatively low (approximately 24%, 503/2086), and the follow-up was limited to once only. Additionally, we could not provide the data of measuring values, such as levels of inflammatory molecules, reactive oxygen species, MT, and endocrine disruptor-related hormones, to clarify the mechanisms of Cd-induced liver damage and the gender susceptibility to the environmental low-dose Cd exposure in this human population study. Therefore, we consider that more comprehensive further studies are needed to reach a definite conclusion in the future. Nevertheless, our results should be meaningful in the management of environmental pollutants by evaluating whether the current Cd exposure can simultaneously affect liver function in the short- and long-term through cross-sectional and longitudinal observations.

In summary, the GM concentration of BCd was 1.07 μg/L in Korean adults, liver injury and the risk of liver damage increased according to the BCd level in both males and

females, and ALT and GGT increased in the relatively high BCd group 4 – 5 years after the baseline study in females but not in males. These findings indicate that environmental Cd exposure can cause liver damage in both the short- and long-term and may be more pronounced in females. Therefore, meticulous control to reduce exposure to Cd by improving individual lifestyles such as smoking, alcohol drinking, and diet habits, and efficient reduction policies of production, release, and use of Cd are necessary to prevent liver-related diseases and to promote public health.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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