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환경적 카드뮴 노출이 간기능에 미치는 영향: 2008-2009 년 국민건강영양조사 자료를 중심으로

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Effects of environmental cadmium exposure on liver function: analysis of KNHANES 2008-2009 data

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ABSTRACT

Introduction: There is inconsistency regarding the effects of cadmium exposure on liver function between the positive results found in animal studies and the negative results highlighted in epidemiological studies. We investigated whether environmental cadmium exposure is associated with an elevation in serum liver enzyme activity in Korean adults.

Methods: This cross-sectional study evaluated adult participants without liver disease from the Korean National Health and Nutrition Examination Survey (KNHANES) for 2008- 2009. Multiple linear regression was conducted to investigate the association between blood cadmium concentration and the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) adjusting for age, sex, body mass index, supplementary health food and the amount of alcohol consumption. Subjects were stratified into quartiles by their cumulative cadmium exposure rank. We estimated the multivariate-adjusted odds ratios (ORs) for liver enzyme

elevation using logistic regression models with the first quartile as the reference group.

Results: Total number of the subjects in the analysis was 3,806. The blood cadmium concentrations were significantly associated with liver enzyme levels (AST, beta=2.844, P-value <.0001; ALT, beta=3.143, P-value <.0001; ALP, beta=8.228, P-value=0.0197). As the cadmium levels approached higher quartiles, the ORs for an elevated AST, ALT and ALP was increased significantly.

Conclusions: Environmental cadmium exposures are associated with an elevation in serum liver enzyme levels in Korean adults.

Keywords: Cadmium, Liver function, Hepatotoxicity, Environmental exposure

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KNHANES: Korean National Health and Nutrition Examination Survey

AST: aspartate transaminase

ALT: alanine aminotransferase

ALP: alkaline phosphatase

BMI: Body mass index

GM: geometric mean

CI: confidence interval

OR: odds ratio

GAM: generalized additive model

AIC: Akaike's information criterion

INTRODUCTION

Cadmium is a widely used metal in many industries. The cadmium emissions to the air, water and soil have been increased dramatically during the twentieth century.[1] This metal is a well-known persistent environmental pollutant.[2]

Once it has been absorbed into the human body, the biological half-life of cadmium is beyond 10 years.[3] It has been reported that the cadmium exposure in population is associated with osteoporosis, renal dysfunction, diabetes, cancer, blood pressure and reproduction.[4]

The greatest body accumulation of cadmium occurs in the liver and kidney. It has been well established that environmental exposure to cadmium may induce kidney dysfunction in the general population. Several studies indicated a higher incidence of renal dysfunction in workers with blood cadmium concentration even below 10 μg/L.[5] For example, Jakubowski et al. reported an increase of low-molecular-mass protein excretion in about 10% of workers having cadmium concentrations in the blood equal to 10 μg/L for 30 to 40 years.[6]

However, less attention has been paid to the possibility that cadmium exposure may also cause dysfunction in the liver. It has previously been shown in experimental animals that cadmium is toxic to the liver after repeated or even a single dose administration.[7-10] However, human studies appear to be scarce. Only a few epidemiologic studies have mentioned the possibility of an association between cadmium exposure and liver dysfunction.[11-14] Most epidemiologic studies to date have reported that there are no significant associations. Toda et al. reported that they did not find any abnormalities in liver function tests (including AST and ALT) among workers who had been exposed to cadmium.[13] Ikeda et al. were unable to find any dose-dependent changes in liver function parameters in women of the general Japanese population.[12] Similarly, the result from NHANES for the USA population did not show a significant relationship between blood cadmium levels and ALT elevation.[11] Overall, there is inconsistency in the observation among the positive results of animal studies and the negative results of epidemiological studies regarding the effects of cadmium exposure on liver function.

It has been reported that the mean blood concentration of cadmium among Koreans (1.27 μg/L) is lower than that for Japanese (2.13 μg/L) but higher than the levels for many other countries, such as German (0.38 μg/L), Begium (0.42 μg/L), Sweden (0.35 μg/L), and USA (0.3 μg/L).[15]

We assumed that the data from a population with higher cadmium levels could provide a better opportunity to evaluate the possible effects on liver. As a result, we investigated whether environmental cadmium exposure is associated with an elevation in serum liver enzyme levels using data from nationally representative population in Korean adults.

MATERIALS AND METHODS

1. Study design and participants

We used data from the Korean National Health and Nutrition Examination Survey (KNHANES) 2008-2009, which was the most recent KNHANES data at the time of analysis. The KNHANES is a cross-sectional, nationally representative survey conducted by the Korean Ministry of Health and Welfare. The target population of the survey was non-institutionalized civilians aged ≥19 years in Korea. Sampling units were households selected through a stratified, multi-stage, probability sampling design based on geographic area, sex, and age group using household registries. About 10,000 subjects from 3,840 households were included in the study every year. Weights indicating the probability of being sampled were assigned to each participant, enabling the results to represent the entire Korean population.

At the time of the KNHANES 2008-2009, citizens were informed they had been randomly selected as a household to

voluntarily participate in the nationally representative survey conducted by the Korean Ministry of Health and Welfare. The participants gave written informed consent for participation in the study.

For our study, we used the following exclusion criteria: age < 18 years, HBsAg (+), other liver disease such as viral hepatitis, liver cirrhosis and liver cancer. A total of 3,994 subjects were evaluated for eligibility, but after applying these exclusion criteria and eliminating other subjects with missing values, the final analyzing sample size was 3,806. (Figure 1)

2. Variables measurement

Participants were asked about lifestyle behaviors, including cigarette smoking, alcohol consumption, and the information of diagnoses and a list of medications being taken. Completed questionnaires were reviewed by trained staff and entered into a database. Smoking exposure was categorized as nonsmoker and current smoker. Alcohol consumption was assessed by asking participants about their drinking behavior during the month prior to the interview. The participants were asked about their average frequency (days per month) of alcohol consumption and average amount (in milliliters) of alcoholic beverages consumed on any single occasion. The responses were converted into the average amount of pure alcohol (in grams) consumed per day.

Participants completed the health examination which consisted of a physical examination, a questionnaire about health-related behavior, and biochemical measurements. Physical examinations were performed by trained medical staff following a standardized procedure. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body

mass index (BMI) was calculated as the ratio of weight (kg)/height (m2).

To assess the levels of liver enzymes and heavy metals in whole blood, 3ml blood samples were drawn into standard commercial evacuated tubes containing sodium heparin (Vacutainers [BD, NJ, USA]). Blood cadmium was measured by graphite furnace atomic absorption spectrometry with Zeeman background correction (PerkinElmer AAnalyst 600/Finland)). Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were analyzed by an auto-biochemical analyzer (Hitachi 7600-II, Hitachi High-Technologies Corporation, Japan). Pureauto S AST (Daiichi pure chemicals, Tokyo, Japan), pureauto S ALT (Daiichi pure chemicals, Tokyo, Japan) and pureauto S ALP (Daiichi Pure Chemicals, Tokyo, Japan) were used as reagents. All blood cadmium and liver enzyme analysis was carried out by Neodin Medical Institute (NMI), a laboratory certified by the Korean Ministry of Health and Welfare. For the internal quality assurance and control program, commercial reference materials were obtained from Bio-Rad (Lyphocheks Whole Blood Metals Control [Bio-Rad, CA, USA]). As part of the external quality

assurance and control, the institute passed both the German External Quality Assessment Scheme operated by Friedrich-Alexander University and the quality assurance program operated by the Korea Occupational Safety and Health Agency. The institute also held a certified license from the Ministry of Labor as one of the designated laboratories for special chemicals including heavy metals and certain organic chemicals.

3. Statistical analysis

Since the concentrations of three liver enzymes and cadmium were not normally distributed, we used their log transformed values for our analysis. The geometric mean (GM) values and 95% confidence interval (CI) were calculated by gender, age group, smoking status, drinking status, supplementary health food and BMI.

We used multiple linear regression analysis to evaluate the relationship between blood cadmium level and three liver enzymes adjusting for age, gender, BMI, supplementary health food and the amount of daily alcohol consumption. In this analysis, we had assumed that the relationship is linear. According to a study conducted in Korea[16], blood cadmium concentrations may have dose-response relationship with daily alcohol intake. As a result, we adjusted alcohol as a continuous value. Smoking is a well-known determinant of cadmium, it might be a potential confounder in the analysis and a sensitivity analysis in non-smokers is therefore essential. Moreover the effect of cadmium on liver function may be affected by gender

or drinking habits. So we performed stratified analysis according to gender, smoking habits and drinking habits.

To calculate the odds ratios, we set a cutoff value for the liver enzyme elevation with the reference value over 35 IU/L for AST, 45 IU/L ALT and 280 IU/L for ALP[17]. After that we set the criteria for clinically significant abnormality for LFT as over 2 times the cutoff value of any one of the liver enzymes. Subjects were stratified into quartiles by their cumulative cadmium exposure rank, with the first quartile representing subjects with the lowest levels. We estimated multivariate-adjusted odds ratios (ORs) for each liver enzyme elevations and clinically significant abnormality using logistic regression models with the first quartile as the reference group. Models were adjusted for age, gender, BMI, supplementary health food and the amount of daily alcohol consumption.

Statistical analyses were performed using SURVEYREGRESSION and SURVEYLOGISTIC in SAS (Version 9.22, SAS Institute, Cary, NC), a software package that incorporates sample weights and adjusts analyses for the complex sample design of the survey. Survey sample weights were used in all analyses to produce estimates that were

representative of the non-institutionalized civilian Korean population. Figures were drawn by using a generalized additive model (GAM) of R version 2.12.2. (The Comprehensive R Archive Network: http://cran.r-project.org) We used a p-value $\leq$ 0.05 to indicate statistical significance.

RESULTS

The mean age (and corresponding SD) was 45.37±15.59 years (range, 19- 87 years) and the geometrical mean of the blood cadmium level was 0.89 μg/L. Approximately a half of the study population was female and one third of the study population was overweight or obese. About one fourth was current smokers and only one fourth of the study populations did not drink alcohol during the month prior to the survey. The blood cadmium concentrations and levels of liver enzymes of the study participants are listed in Table 1 by age, gender, BMI, smoking and drinking status.

Figure 2 shows the relations between blood cadmium levels and serum liver enzyme levels. Blood cadmium levels were positively associated with serum liver enzyme levels. These results are statistically significant based on simple and multiple linear regression analysis. (Table 2) When we adjusted for age, sex, BMI and daily alcohol consumption, AST (β=2.844; p-value<.0001), ALT (β=3.143; p-value<.0001) and ALP (β=8.228; p-value<.0001) had statistically significant

associations with the blood cadmium level. We also found a statistically significant association between the log transformed values of liver enzymes and cadmium. Adjusting for age, sex, BMI, supplementary health food and daily alcohol consumption, most of the p-value remained below 0.05. The results of the stratified analysis by smoking habits, gender and drinking habits are summarized in Table 4-9. The effect of cadmium on serum ALP level was modified by the smoking habits, gender and drinking habits. In the final models non-smokers, smoker, drinkers and women did not show the statistically significant relationship between serum ALP levels and blood cadmium level or log transformed value of it even though the relationship in non-drinker and men was still significant.

To evaluate the association of blood cadmium level and the prevalence of elevated liver enzyme, the OR and 95% CI values for elevated liver enzyme with cadmium levels stratified into quartiles after adjustment for covariates were calculated. As the cadmium levels approached the higher quartiles, the ORs for elevated AST, ALT and ALP increased significantly but ORs for clinically significant abnormality for LFT was not statistically significant. (p-value=0.197) (Table 3)

DISCUSSION

The potential sources of cadmium exposure in this population may be mostly environmental. Cadmium concentrations in the blood increase with aging, cigarette smoking, and increasing exposure to environmental pollution.[18] Elinder reviewed a number of studies measuring blood cadmium concentration of non-occupationally exposed persons and concluded that, in countries where dietary cadmium intake is between 10 and 20 μg/day, nonsmokers have a median cadmium blood concentration between 0.4 and 1.0 μg/L, and smokers have median concentration between 1.4 and 4.5 μg/L.

In a general population survey of approximately 4,700 adults in Germany, Becker and colleagues found geometric mean cadmium levels of 0.44 μg/L in the blood,[19] and 0.23 μg/L in the urine.[20] A study by the Centers for Disease Control and Prevention in the USA based on data from a complex multistage probability sample found that the mean blood concentration of cadmium was 0.41 μg/L (n = 7970), and the 95th percentile

blood concentration was 1.3 μg/L.[19] In the present study, the mean concentration of blood cadmium stood at 0.94 μg/L was higher compared to the results from Germany and USA. This is partially because Korean people are exposed to high levels of cadmium through the intake of foods including rice.[12, 22] In the study conducted to assess cadmium burden in the general Korean populations, the geometric mean for dietary cadmium intake was 21.2 μg/day, which is much larger amount than many other countries, and cadmium intake form boiled rice accounted for 23% of total daily cadmium intake.[23]

Smoke inhalation is one of the major exposure routes because one cigarette produced in Korea contains approximately 0.75 μg of cadmium.[24] Many researchers have estimated that 10 to 20% of the total cadmium in cigarettes is inhaled from smoking.[15, 25-26] By applying this range of inhalation rates, the amount of cadmium inhaled from smoking can be estimated to be 1.5 to 3.0 μg/pack. In this reason, we thought of smoking as not a confounder but instead one of the primary exposure routes. However, we presented the results of analysis adjusting for smoking as well on Table 3, but no significant changes in the results were noted.

Possible effects of cadmium on the liver were examined in animal experiments mostly in the 1980s. For example, after the laboratory rats were put single intraperitoneal injection of $CdCl_2$ at a large dose of 3.9 mg/kg,[8] severe liver injury was observed in rats. In repeated administration experiments, serum ALT and AST activities were elevated time-dependently when a subcutaneous injection of $CdCl_2$ was given to the rat at a dose of 0.5 mg/kg, 6 days/week for up to 26 weeks.[7] Similarly, when rats were given a diet containing $CdCl_2$ at 200 mg/kg diet for 26 weeks[9] or CdO at 7.15 mg/kg diet for 40 days,[10] serum AST or both AST and ALT were elevated. In case of isolated rat hepatocytes in vitro,[27] suppressive effects of cadmium were also presented on albumin secretion.

There have been numerous investigations on the mechanism of cadmium-mediated hepatotoxicity. While some uncertainties persist, sufficient evidence has emerged to provide a reasonable account of the toxic process in liver. Hepatotoxicity involves two pathways,[28] one for the initial injury produced by direct effects of cadmium and the other for the subsequent injury produced by inflammation. Primary injury appears to be caused by the binding of Cd^{2+} to sulfhydryl groups on critical

molecules in mitochondria. The inactivation of thiol group can cause oxidative stress, the mitochondrial permeability transition and mitochondrial dysfunction. Although cadmium may injure hepatocytes directly, it is also plausible that hepatocellular injury may be caused by the result of ischemia induced by endothelial cells damage.[29-30]

Secondary injury from acute cadmium exposure is mediated from the activation of Kupffer cells and subsequent events involving several types of liver cells and a large number of inflammatory and cytotoxic mediators. In this toxic process, Kupffer cell activation and neutrophil infiltration play an important role. Involvement of proinflammatory cytokines during this process may also be important.[31]

The primary purpose of this study was to determine whether blood cadmium levels were associated with elevated liver enzyme concentrations in the Korean population who have relatively high blood cadmium levels. In our study, we found positive associations between all the three liver enzyme concentrations and blood cadmium concentrations. We also found increased odds ratios for liver dysfunction with blood cadmium levels. To observe the threshold effect, we consider

the piece-wise linear regression model, which produce two regression lines by the threshold.[32] These two lines are enforced to meet at the threshold value. We estimated the location of the threshold by implementing a grid search and by identifying the Cd level that minimize AIC (Akaike's Information Criterion) values. Figure 2 shows the nonlinear relations between blood Cd levels and serum liver enzyme levels. From the figure, it is evident that a threshold point exists. So, we adapt the threshold Model. Each of the threshold levels of blood Cd are 0.5488 μg/L for AST, 0.2231 μg/L for ALT and 0.4493 μg/L for ALP. (Figure 3)

However, previously reported epidemiological studies have shown inconsistent results. Toda et al. studied 22 cadmium-exposed male factory workers, including 5 workers who were exposed to CdO fumes and excreted 95.6±184.9μg cadmium in urine per day.[13] Similarly, Nordberg et al. observed in an epidemiology study in a Cadmium-polluted area that AST and ALT were normal in 13 cases, although the subjects excreted up to 10.7 μg /L in urine.[14] Ikeda et al. also reported that no cadmium dose-dependent changes in liver function parameters were observed in women in the general Japanese population

subjected to environmental exposure to cadmium at various levels.[12] In a recent study conducted in United States, Cave et al. investigated the relationship between blood cadmium levels and serum ALT levels from the NHANES 2003−2004.[11] They reported they found no significant relationship between the two.

However, a study on the pollution of Lake Manzala in the Nile Delta, Egypt[33] reported that serum AST and ALT levels of the fishermen were elevated, and their blood cadmium levels were also found to be higher than those of controls. It is, however, difficult to link cadmium exposure as the cause of the observed AST and ALT elevation, because the lake water was also contaminated with other metals and pollutants.

Overall, there is inconsistency in the observation of liver dysfunction between the present study and the other epidemiologic studies. Several possibilities may be postulated to explain the discrepancy. One possible explanation is the difference in the exposed cadmium levels. The study by Cave et al. showed a mean cadmium level of 0.30 μg/L for the 1st quartile, 0.40 μg/L for the 2nd quartile, 0.60 μg/L for the 3rd quartile and 1.10 μg/L for the 4th quartile. However, in our study the mean of total participant was 0.89$\pm$0.68 μg/L and the

mean of each quartile was 0.41±0.15 μg/L, 0.81±0.10 μg/L, 1.18±0.13 μg/L and 1.98±0.70 μg/L in ascending quartiles. As seen in Figure 2, the effect of cadmium on liver function is larger at higher levels of blood cadmium. In some aspect, the result of study by Cave et al. is in the same context with our study. Their result shows that for the upper quartiles of cadmium, the OR was increased even though insignificant. (OR=1.2 (95% CI= 0.8−1.7) for third quartile, OR=1.2 (95% CI= 0.7−2.0) for forth quartile)

Another possibility comes from the sample size of the studies. The mean blood cadmium level (1.76 μg/L) in the study by Ikeda et al. is higher than our study but a smaller number of participants were included for the analyses (N=607). As a result, the study is less powered, possibly leading to statistically insignificant result. In the same context we assume that if the study by Cave et al. (N=2051) has a larger sample size, the OR may have a narrower CI and the authors could show significant association.

Several potential problems are inherent to the design of this study. First, the exact specificity of AST, ALT and ALP for liver disease in KNHANES is unknown because we assume the

liver function only by the serum liver enzyme levels. Considering the case of normal liver enzyme levels in liver dysfunction, we may have under-estimated the risk of low-level environmental cadmium exposure on liver disease in the general Korean population. Second, KNHANES did not include an occupation/job code to screen cadmium-exposure jobs such as smelting, iron/steel production, and mining. Therefore, the effect of occupations associated with high dose cadmium exposure was not assessed.

Nevertheless, the present study has some strength. First of all, the study was performed in a representative sample of the general Korean population. Second, strict quality control of study procedures in KNHANES was assured and relatively trace levels of blood cadmium could be measured. Third, the large sample size with relatively higher blood cadmium levels compared to other studies provided better opportunity to evaluate the cadmium effect on the liver in a general population.

CONCLUSION

In summary, cadmium exposures are associated with an elevated liver enzyme level based on the data representative of the Korean adult population. Prevention of cadmium exposure, for example in cigarette smoking or environmental and occupational exposures, could reduce the potential for the development of preclinical liver dysfunction, which may have important implications for health policy and disease prevention.

Table 1. General characteristics, blood cadmium and liver enzyme levels of the study population.

Demographic variable	No. (%)	Mean Cd levels ±SD (μg/L)	Mean AST levels ±SD (IU/L)	Mean ALT levels ±SD (IU/L)	Mean ALP levels ±SD (IU/L) (N=1954)
Sex					
Male	1899(49.9)	0.86±0.64	24.51±16.54	26.94±18.78	228.98±61.38
Female	1907(50.1)	1.02±0.74	19.88±9.01	17.40±12.64	213.72±71.96
Age(years)					
<30	1038(27.27)	0.68±0.62	20.58±17.15	20.54±17.22	211.96±58.87
30-39	688(18.08)	0.84±0.62	20.95±9.11	22.94±18.47	202.62±57.62
40-49	686(18.02)	1.03±0.62	22.06±11.29	22.55±15.09	200.86±52.36
50-59	666(17.50)	1.19±0.75	24.49±13.50	24.98±18.52	245.12±70.98
60-69	421(11.06)	1.16±0.70	23.61±15.14	21.78±14.45	246.59±78.52
≥70	307 (8.07)	1.25±0.70	23.77±10.05	19.46±10.78	253.61±79.76
BMI (kg/m^2)					

<25	2626(69.00)	0.92±0.70	21.29±14.35	19.18±13.85	217.88±65.81
≥25	1180(31.00)	0.97±0.71	24.20±11.17	28.79±20.22	229.12±69.90
Smoking					
Yes	982(25.80)	1.12±0.72	24.49±18.65	26.68±19.28	230.35±60.69
No	2824(74.20)	0.88±0.69	21.39±11.07	20.59±15.39	218.24±69.18
Alcohol drinking					
Yes	2842(74.7)	0.89±0.68	22.58±14.79	22.76±17.40	216.17±65.40
No	964(25.3)	1.06±0.76	21.06±8.61	20.41±14.27	237.17±70.54
Overall	3806(100)	0.93±0.70	22.20±13.51	22.17±16.69	221.35±67.29

Table 2. Linear regression model analysis results for liver enzyme levels.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	2.9082	0.3788	0.0235	<.0001	0.1117	0.0101	0.0427	<.0001
Model 2	2.8400	0.4044	0.0664	<.0001	0.0961	0.0110	0.1398	<.0001
Model 3	2.8437	0.4901	0.0872	<.0001	0.0783	0.0129	0.2030	<.0001
Model 4	3.1293	0.5706	0.0881	<.0001	0.0972	0.0143	0.2090	<.0001
ALT								
Model 1	1.8213	0.4046	0.0050	<.0001	0.1110	0.0150	0.0166	<.0001
Model 2	3.0090	0.0230	0.0922	<.0001	0.1407	0.0007	0.1723	<.0001
Model 3	3.1432	0.6381	0.2003	<.0001	0.1196	0.0203	0.3232	<.0001
Model 4	3.0133	0.7273	0.2004	<.0001	0.1110	0.0212	0.3233	<.0001
ALP								
Model 1	14.9596	2.4831	0.0236	<.0001	0.0608	0.0100	0.0216	<.0001
Model 2	9.4765	2.6531	0.0808	0.0005	0.0365	0.0005	0.0894	0.0008
Model 3	8.2282	3.4969	0.0868	0.0197	0.0247	0.0134	0.1020	0.0660
Model 4	7.1321	3.8295	0.0875	0.0642	0.0334	0.0149	0.1067	0.0267

Model1 is not adjusted.

Model2 is adjusted for age and sex.

Model3 is adjusted for age, sex, BMI, supplementary health food and daily alcohol consumption.

Model4 is adjusted for age, sex, BMI, supplementary health food , daily alcohol consumption and the amount of smoking.

Table 3. ORs(95% CIs) for AST, ALT, and ALP elevation and clinically significant abnormality for liver function tests by exposure quartile for cadmium in adults, KNHANES 2008–2009

quartile	1st	2nd	3rd	4th	p-trend
Mean Cd levels ±SD (μg/L)	0.44±0.15	0.81±0.10	1.18±0.13	2.05±0.69	
Elevated AST[a]					
Mean AST levels ±SD (IU/L)	20.16±11.63	21.92±12.06	21.94±9.97	24.77±18.43	
No. of cases	39/956	57/948	44/952	111/950	251/3806
OR(95% CI)	Referent	1.15(0.63-2.09)	1.43(0.79-2.56)	3.11(1.87-5.19)	<.0001
Elevated ALT[a]					
Mean ALT levels ±SD (IU/L)	20.36±15.40	23.18±19.06	21.40±14.71	23.73±17.09	
No. of cases	59/956	84/948	54/952	79/950	276/3806
OR(95% CI)	Referent	1.35(1.83-2.19)	1.34(0.78-2.36)	2.30(1.40-3.75)	0.0024
Elevated ALP[a]					
Mean ALP levels ±SD (IU/L)	206.18±59.95	216.95±66.86	226.54±70.46	235.04±67.76	
No. of cases	46/450	54/479	83/483	111/486	294/1898

OR(95% CI)	Referent	0.069(0.37-1.15)	1.08(0.61-1.93)	2.16(1.29-3.61)	0.0018
Clinically significant elevation of LFTs[b]					
No. of cases	5/450	10/479	5/483	11/486	31/1898
OR(95% CI)	Referent	1.56(0.37-6.56)	0.58(0.09-3.47)	3.05(0.82-11.30)	0.1970

[a] We set a cutoff value for the liver enzyme elevation with the reference value over 35 IU/L for AST, 45 IU/L ALT and 280 IU/L for ALP.

[b] We set the criteria for clinically significant abnormality for LFT as over 2 times the cutoff value of any one of the liver enzymes.

Table 4. Sub-analysis results for liver enzyme levels in non-smokers only using the linear regression model.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	1.5838	0.2605	0.0103	<.0001	0.0802	0.0094	0.0278	<.0001
Model 2	1.7777	0.3477	0.0660	<.0001	0.0781	0.0005	0.1484	<.0001
Model 3	1.9243	0.4719	0.0964	<.0001	0.0629	0.0027	0.2141	<.0001
ALT								
Model 1	0.2771	0.3590	0.0001	0.4406	0.0609	0.0164	0.0058	<.0001
Model 2	2.1220	0.5227	0.0843	<.0001	0.1163	0.0191	0.1701	<.0001
Model 3	2.0550	0.7282	0.1924	0.0050	0.0868	0.02152	0.3200	<.0001
ALP								
Model 1	15.8421	3.1888	0.0220	<.0001	0.0560	0.0119	0.0180	<.0001
Model 2	7.7774	3.4986	0.0832	0.0275	0.0236	0.0131	0.0869	0.0747
Model 3	7.2169	4.1507	0.0869	0.0838	0.0255	0.0135	0.1022	0.0683

Model1 is not adjusted.

Model2 is adjusted for age, sex and supplementary health food.

Model3 is adjusted for age, sex, BMI, supplementary health food and daily alcohol consumption.

Table 5. Sub-analysis results for liver enzyme levels in smokers only using the linear regression model.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	5.6182	1.1724	0.0406	<.0001	0.1827	0.0277	0.0624	<.0001
Model 2	5.3895	1.2836	0.0545	<.0001	0.1634	0.0283	0.1028	<.0001
Model 3	3.7684	0.8328	0.0956	<.0001	0.1306	0.0284	0.2003	<.0001
ALT								
Model 1	5.1874	2.3770	0.0145	0.0298	0.1567	0.0356	0.0227	<.0001
Model 2	6.8623	2.8815	0.0346	0.0178	0.2047	0.0392	0.0914	<.0001
Model 3	3.8808	1.0111	0.1734	0.0001	0.1990	0.0359	0.2806	<.0001
ALP								
Model 1	12.0056	4.9979	0.0204	0.0174	0.0527	0.0236	0.0136	0.0272
Model 2	9.6332	5.2868	0.0589	0.0703	0.0395	0.0252	0.0638	0.1186
Model 3	9.6236	5.0964	0.0670	0.0608	0.0421	0.0264	0.0775	0.1120

Model1 is not adjusted.

Model2 is adjusted for age, sex and supplementary health food.

Model3 is adjusted for age, sex, BMI, supplementary health food and daily alcohol consumption.

Table 6. Linear regression model analysis results for liver enzyme levels in men only.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	5.1305	0.9122	0.0251	<.0001	0.1372	0.0153	0.0443	<.0001
Model 2	4.923	0.9665	0.0649	<.0001	0.1184	0.0161	0.1415	<.0001
Model 3	3.7142	0.6696	0.0658	<.0001	0.0875	0.0161	0.1491	<.0001
Model 4	4.1360	0.8242	0.0667	<.0001	0.1009	0.0185	0.1509	<.0001
ALT								
Model 1	4.8709	1.8503	0.0139	0.0088	0.1381	0.0230	0.0260	<.0001
Model 2	5.9216	2.0846	0.0198	0.0047	0.1546	0.0247	0.0286	<.0001
Model 3	4.0578	0.8636	0.1485	<.0001	0.1363	0.0238	0.2211	<.0001
Model 4	4.0710	1.0227	0.1485	<.0001	0.1250	0.0289	0.3035	<.0001
ALP								
Model 1	14.7534	3.8298	0.0243	0.0002	0.0526	0.0148	0.0197	0.0005
Model 2	14.0710	3.8127	0.0240	0.0003	0.0529	0.0147	0.0197	0.0004
Model 3	12.6126	3.7119	0.0276	0.0008	0.0483	0.0151	0.022	0.0017
Model 4	10.6435	4.4733	0.0290	0.0184	0.0450	0.0178	0.0276	0.0126

Model1 is not adjusted.

Model2 is adjusted for age.

Model3 is adjusted for age, BMI, supplementary health food and daily alcohol consumption.

Model4 is adjusted for age, BMI, supplementary health food , daily alcohol consumption and the amount of smoking.

Table 7. Linear regression model analysis results for liver enzyme levels in women only.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	2.4667	0.3602	0.045	<.0001	0.1332	0.0125	0.0793	<.0001
Model 2	1.4556	0.3797	0.0747	<.0001	0.0676	0.0133	0.1338	<.0001
Model 3	1.6023	0.5294	0.0967	<.0001	0.0533	0.0156	0.1580	0.0007
Model 4	1.6556	0.5269	0.0895	0.0018	0.0559	0.01535	0.1587	0.0003
ALT								
Model 1	2.5461	0.4304	0.0237	<.0001	0.1881	0.0124	0.0652	<.0001
Model 2	1.619	0.4797	0.0361	0.0008	0.1141	0.0213	0.0938	<.0001
Model 3	1.8876	0.6830	0.1162	0.0060	0.0938	0.0261	0.3034	0.0004
Model 4	1.739	0.6529	0.1179	0.0081	0.0968	0.0243	0.2098	<.0001
ALP								
Model 1	21.2162	3.5104	0.04347	<.0001	0.0989	0.0148	0.0465	<.0001
Model 2	2.5978	3.5679	0.1688	0.4675	0.0085	0.0163	0.1707	0.5997
Model 3	0.9492	4.6875	0.1366	0.8398	0.0009	0.0165	0.1381	0.5781
Model 4	0.1931	4.7351	0.1383	0.9675	0.0126	0.0171	0.1401	0.4614

Model1 is not adjusted.

Model2 is adjusted for age.

Model3 is adjusted for age, BMI, supplementary health food and daily alcohol consumption.

Model4 is adjusted for age, BMI, supplementary health food , daily alcohol consumption and the amount of smoking.

Table 8. Linear regression model analysis results for liver enzyme levels in drinkers only.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	5.3208	1.0020	0.0408	<.0001	0.1671	0.0230	0.0738	<.0001
Model 2	5.0241	0.9401	0.0728	<.0001	0.1519	0.0219	0.1582	<.0001
Model 3	5.0897	0.9571	0.0744	<.0001	0.1528	0.0221	0.1740	<.0001
Model 4	4.7319	1.0991	0.0751	<.0001	0.1506	0.0238	0.1741	<.0001
ALT								
Model 1	3.8637	0.8564	0.0240	<.0001	0.1583	0.0311	0.0338	<.0001
Model 2	4.6074	0.8296	0.0903	<.0001	0.1798	0.0314	0.1543	<.0001
Model 3	4.5800	0.8891	0.1558	<.0001	0.1776	0.0296	0.2546	<.0001
Model 4	4.1288	0.9749	0.1571	<.0001	0.1692	0.0340	0.2550	<.0001
ALP								
Model 1	3.3763	3.9149	0.0014	0.3898	0.0151	0.0179	0.0014	0.4000
Model 2	6.0854	3.8705	0.0757	0.1179	0.0293	0.0183	0.0998	0.1220
Model 3	6.1393	3.7967	0.0809	0.1079	0.0302	0.0184	0.1024	0.1025
Model 4	0.5094	4.5119	0.0926	0.9103	0.0042	0.0205	0.1153	0.8378

Model1 is not adjusted.

Model2 is adjusted for age and sex.

Model3 is adjusted for age, sex, BMI and supplementary health food.

Model4 is adjusted for age, sex, BMI, supplementary health food and the amount of smoking.

Table 9. Linear regression model analysis results for liver enzyme levels in non-drinkers only.

	Crude values				log transformed values			
	Estimate	**Std. error**	**R-square**	**p-value**	**Estimate**	**Std. error**	**R-square**	**p-value**
AST								
Model 1	2.2011	0.4827	0.0166	<.0001	0.0886	0.0109	0.0307	<.0001
Model 2	2.1268	0.6005	0.0485	0.0004	0.0660	0.0125	0.1128	<.0001
Model 3	2.0337	0.5967	0.0656	0.0007	0.0601	0.0121	0.1490	<.0001
Model 4	2.2133	0.5756	0.0667	0.0001	0.0708	0.0121	0.1518	<.0001
ALT								
Model 1	1.8758	1.1558	0.0032	0.1054	0.0881	0.0177	0.0107	<.0001
Model 2	3.7327	1.5479	0.0571	0.0164	0.1269	0.0197	0.1550	<.0001
Model 3	3.3931	1.5319	0.1255	0.0274	0.1103	0.0180	0.2985	<.0001
Model 4	3.1942	1.4079	0.1261	0.0238	0.1105	0.0186	0.2992	<.0001
ALP								
Model 1	20.7616	2.9907	0.0424	<.0001	0.0807	0.0119	0.0363	<.0001
Model 2	13.8279	3.2956	0.1111	<.0001	0.0498	0.0134	0.1167	0.0003
Model 3	13.6154	3.3420	0.1135	<.0001	0.0486	0.0135	0.1203	0.0004
Model 4	12.2338	3.4474	0.1163	0.0005	0.0410	0.0142	0.1235	0.0043

Model1 is not adjusted.

Model2 is adjusted for age and sex.

Model3 is adjusted for age, sex, BMI and supplementary health food.

Model4 is adjusted for age, sex, BMI, supplementary health food and the amount of smoking.

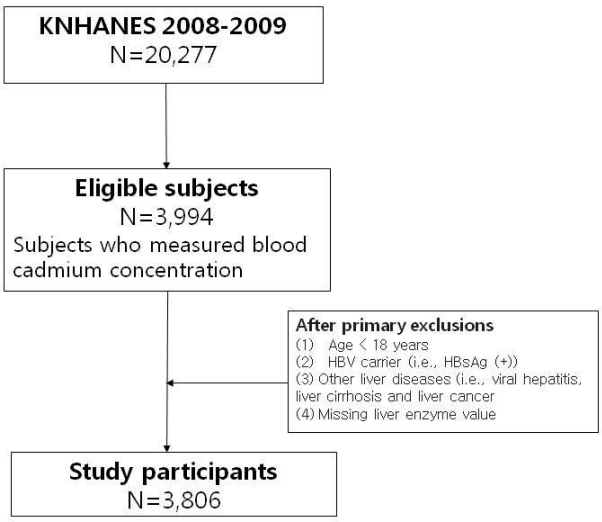

Figure 1. Schematic diagram depicting study population.

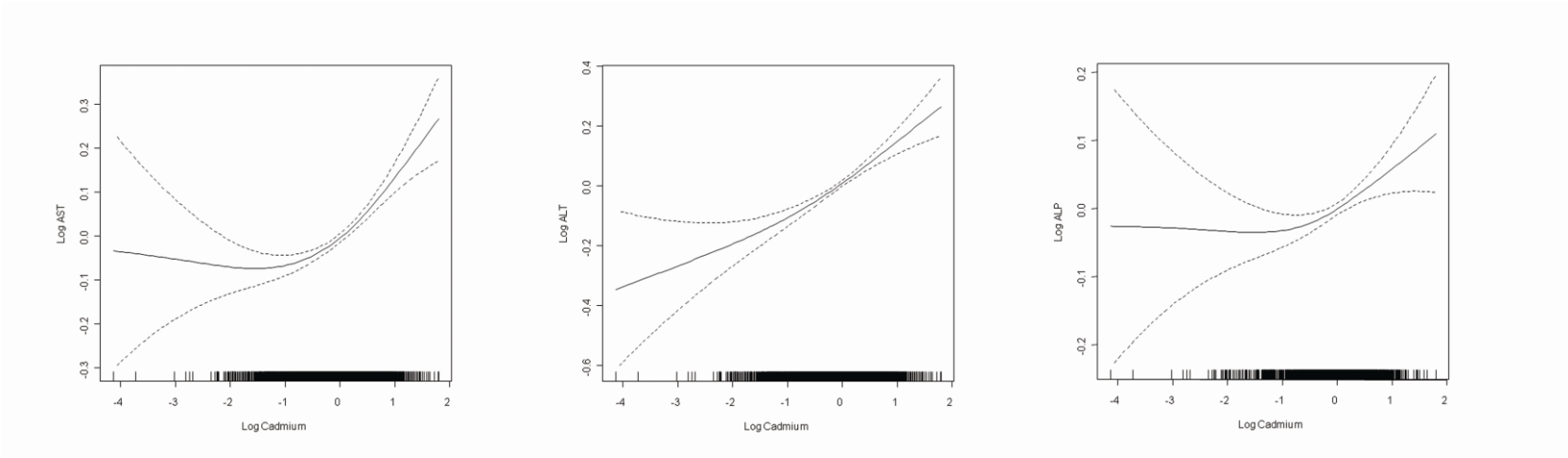

Figure 2. Generalized additive model of log transformed value of cadmium and three liver enzymes.

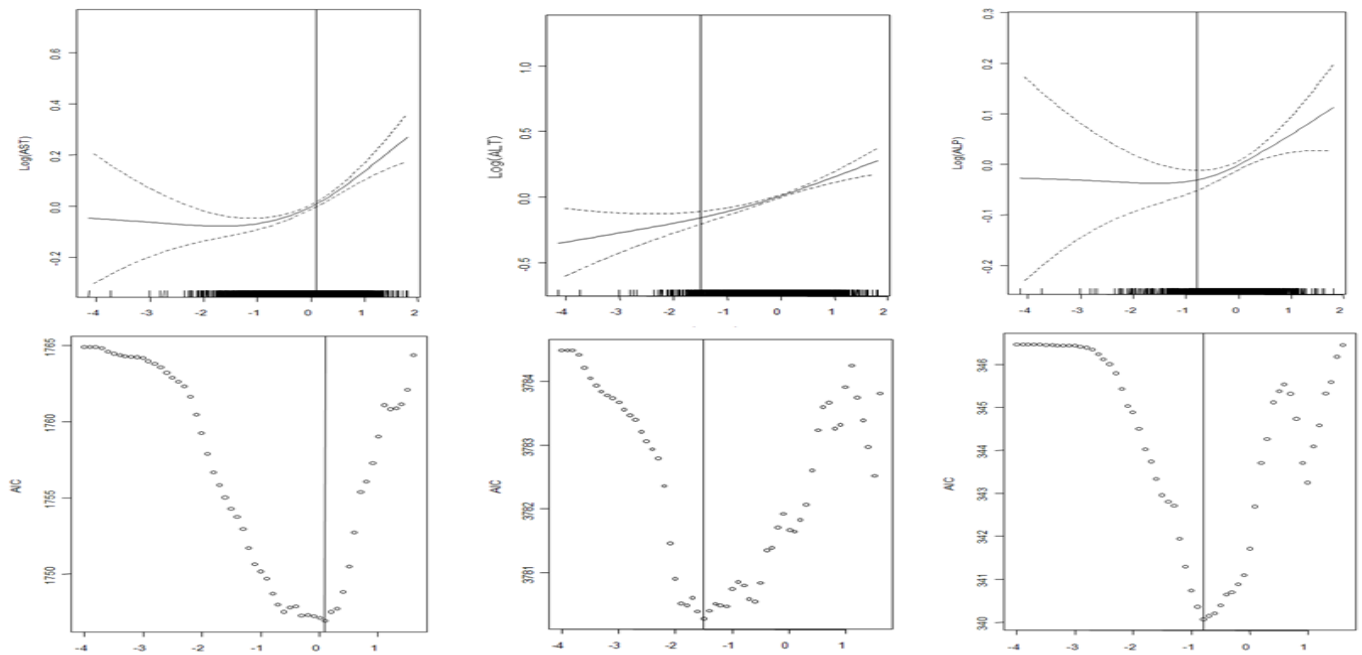

Figure 3. The estimated threshold of cadmium level which affects elevation of liver enzymes and minimize AIC value.

REFERENCES

1. Järup L, Berglund M, Elinder CG, *et al.* Health effects of cadmium exposure—a review of the literature and a risk estimate. *Scand J Work Environ Health*. 1998;**24**:1—51.
2. World Health Organization. 1972. Long term programme in environmental pollution control in Europe. *The hazards to health of persistent substances in water Annexes to a report on a working group Technical documents on arsenic, cadmium, lead, manganese and mercury.* Copenhagen.
3. World Health Organization. 1992. International Programme on Chemical Safety Environmental health criteria 134. Cadmium. Geneva
4. Nawrot, T. S., J. A. Staessen, et al. (2010). "Cadmium exposure in the population: from health risks to strategies of prevention." Biometals 23(5): 769—782.
5. American Conference of Governmental Industrial Hygienists. 2005. Cadmium and compounds BEI. In: TLVs and BEIs with 7th Edition Documentation. ACGIH, Cincinnati.

6. Jakubowski M, Trojanowska B, Kowalska G, *et al.* Occupational exposure to cadmium and kidney dysfunction. *Int Arch Occup Environ Health*. 1987;59:567-577.
7. Dudley RE, Gammal LM, Klaassen CD. Cadmium-induced hepatic and renal injury in chronically exposed rats: likely role of hepatic cadmium-metallothionein in nephrotoxicity. *Toxicol Appl Pharmacol*. 1985;77:414-426.
8. Dudley RE, Svoboda DJ, Klaassen CD. Acute exposure to cadmium causes severe liver injury in rats. *Toxicol Appl Pharmacol*. 1982;65:302-313.
9. Nakamura K, Nishiyama S, Takata T, *et al.* Effects of zinc on cadmium-induced alterations in hepatic functions and blood glucose of rats. *Environ Res*. 1983;30:175-181.
10. Weigel H, Elmadfa I, Jäger H. The effect of low doses of dietary cadmium oxide on the disposition of trace elements (zinc, copper, iron), hematological parameters, and liver function in rats. *Arch Environ Contam Toxicol*. 1984;13:289-296.
11. Cave M, Appana S, Patel M, *et al.* Polychlorinated Biphenyls, Lead, and Mercury Are Associated with Liver Disease in American Adults: NHANES 2003- 2004. *Environ Health Perspect*. 2010;118:1735.

12. Ikeda M, Zhang ZW, Moon CS, *et al.* Normal liver function in women in the general Japanese population subjected to environmental exposure to cadmium at various levels. *Int Arch Occup Environ Health*. 2000;**73**:86-90.

13. Toda K, Mori K, Koike S, *et al.* Chronic renal dysfunction in workers exposed to cadmium oxide fumes (in Japanese with English abstract). Sangyo Igaku 1984;**26**:212-213

14 Nordberg GF, Jin T, Kong Q, *et al.* Biological monitoring of cadmium exposure and renal effects in a population group residing in a polluted area in China. *Sci Total Enviro*n 1997;199: 111-114

15 CONTAM . 2009. Scientific opinion of the panel on contaminants in the food chain on a request from the European commission on cadmium in food. EFSA J 980:1- 139

16. Lee B, Ha J. The Effects of Smoking and Drinking on Blood Lead and Cadmium Levels: Data from the Fourth Korea National Health and Nutrition Examination Survey. *Korean Journal of Occupational and Environmental Medicine*. 2011;**23**:31-41.

17. Limdi, J. and G. Hyde. "Evaluation of abnormal liver function tests." Postgraduate Medical Journal 2003; 79(932): 307-312.

18 Elinder C. Normal values for cadmium in human tissues, blood, and urine in different countries. *Cadmium and health: A toxicological and epidemiological appraisal*. 1985;**1**:81-102.

19. Becker K, Kaus S, Krause C, *et al.* German Environmental Survey 1998 (GerES III): environmental pollutants in blood of the German population. *International journal of hygiene and environmental health*. 2002;**205**:297-308.

20. Becker K, Schulz C, Kaus S, *et al.* German Environmental Survey 1998 (GerES III): environmental pollutants in the urine of the German population. *International journal of hygiene and environmental health*. 2003;**206**:15-24.

21. Centers for Disease Control and Prevention. 2005. Third National Report on Human Exposure to Environmental Chemicals. US Department of Health and Human Services, Public Health Services. Available : http://www.cdc.gov/exposurereport/.

22. Moon CS, Paik JM, Choi CS, *et al.* Lead and cadmium levels in daily foods, blood and urine in children and their mothers in Korea. *Int Arch Occup Environ Health*. 2003;**76**:282-288.

23. Moon CS, Zhang ZW, Shimbo S, *et al.* Dietary intake of cadmium and lead among the general population in Korea. *Environ Res*. 1995;**71**:46-54.

24. Jung M, Thornton I, Chon H. Arsenic, cadmium, copper, lead, and zinc concentrations in cigarettes produced in Korea and the United Kingdom. *Environmental technology*. 1998;**19**:237-241.

25. Nordberg GF, Nogawa K, Nordberg M et al. 2007. Cadmium. In: Nordberg GF, Fowler BF, Nordberg M et al (eds) Handbook on the toxicology of metals. Elsevier, Amsterdam, pp 445- 486

26. Yeon YY, Ahn KD, Lee BK. Blood and urine cadmium levels in non-exposed Korean to cadmium. *Korean Journal of Occupational and Environmental Medicine*. 1992;**4**:70-80.

27. Wan X, Lachapelle M, Marion M, *et al.* Recovery potential of hepatocytes from inhibition of albumin secretion by cadmium. *J Toxicol Environ Health*. 1993;**38**:381-392.

28. Rikans LE, Yamano T. Mechanisms of cadmium-mediated acute hepatotoxicity. *J Biochem Mol Toxicol*. 2000;**14**:110-117.

29. Liu J, Kershaw W, Liu Y, Klaassen C. Cadmium-induced hepatic endothelial cell injury in inbred strains of mice. *Toxicology*. 1992;**75**:51-62.

30. Nolan CV, Shaikh ZA. The vascular endothelium as a target tissue in acute cadmium toxicity. *Life Sci*. 1986;**39**:1403-1409.

31. Sauer JM, Waalkes MP, Hooser SB, *et al.* Suppression of Kupffer cell function prevents cadmium induced

hepatocellular necrosis in the male Sprague-Dawley rat. *Toxicology*. 1997;**121**:155-164.

32. Kim SY, Lee JT, Hong YC, Ahn KJ, Kim H. Determining the threshold effect of ozone on daily mortality: an analysis of ozone and mortality in Seoul, Korea, 1995-1999. *Environmental research* 2004; 94(2):113-119.

33. Osfor M, El-Dessouky S, El-Sayed A, *et al.* Relationship between environmental pollution in Manzala Lake and health profile of fishermen. *Food/Nahrung*. 1998;**42**:42-45.

국문 초록

배경: 카드뮴은 음식물과 흡연을 통해 우리 몸에 흡수되어 신장, 간 등에 주로 침착된다. 카드뮴이 신장기능에 장애를 초래할 수 있다는 점은 많은 연구를 통하여 일관되게 보고되고 있는데 반하여, 간기능 이상이 초래되는지에 대해서는 동물실험에서는 유의미한 상관관계가 보고되고 있으나, 인간을 대상으로한 역학연구에서는 그렇지 못하다. 이에 저자들은 제 4 기 국민영양조사 자료를 이용하여 저농도 카드뮴 노출이 간기능 이상과 연관되어 있는지를 평가하였다.

방법: 제 4 기 국민영양건강조사 자료 중 분석 당시 이용 가능하였던 2008 년과 2009 년 자료를 이용하였다.측정된 3 가지 간기능 검사 수치는 aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) 였고, 혈중에서 측정한 카드뮴 농도와의 상관성을 파악하기 위해 나이, 성별, 체질량지수, 술 섭취량 등을 보정하여 다중선형회귀분석을 실시하였다. 또한 피험자를 혈중 카드뮴 농도에 따라 사분위로 나눈 후 간효소 수치가 정상 참고치 이상으로 높아진 군의 비율을 비교하였고, 이를 바탕으로 오즈비를 산출하였다.

결과: 총 3914 명이 분석에 활용되었고, 혈중 카드뮴 농도는 각 간효소 수치와 유의하게 연관되어 있었다. (AST, beta=2.677, P-value <.0001; ALT, beta=3.696, P-value <.0001; ALP, beta=11.730, P-value <.0001) 또한 로지스틱 회귀분석 결과 카드뮴 농도가 가장 낮은 사분위군과 비교하여 농도가 점차 높은 군으로 갈수록 간기능이 정상이상으로 증가될 오즈비가 통계적으로 유의하게 증가하였다.

결론: 한국성인에서 저농도의 카드뮴 노출은 간기능 이상과 연관되어 있다.

주요어 : 카드뮴, 간기능 장애, 환경적 노출, 간독성
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