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Association of blood pressure with blood lead and cadmium levels in Korean adolescents: Analysis of data from the 2010–2016 Korean National Health and Nutrition Examination Survey

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Abstract

We evaluated the association of blood pressure with blood levels of cadmium, lead, and cadmium and lead together (cadmium+lead) in a representative sample of adolescents from Korea by use of 2010-2016 data from the Korean National Health and Nutrition Examination Survey (KNHANES). This cross-sectional study enrolled adolescents aged at 10-18 years-old who completed a health examination survey and had blood measurements of lead and cadmium. The association of adjusted mean differences in diastolic and systolic blood pressure with doubling of blood lead and cadmium were estimated by regression of blood pressure against $\log_2$-transformed blood metals and their quartiles after covariate adjustment. Adjusted odds ratios for prehypertension were calculated for $\log_2$-transformed blood levels of lead and cadmium and their quartiles. Our analysis of adolescents in Korea indicated that blood levels of lead and cadmium were not significantly associated with increased blood pressure or risk of pre-hypertension. However, the cadmium+lead level was associated with pre-hypertension. Previous studies showed that blood levels of lead and cadmium were associated with increased blood pressure and risk of hypertension in adult populations. We found no such effect in Korean adolescents, although the cadmium+lead level was associated with prehypertension. These differences may be because adolescents generally have lower levels of these blood metals or because adolescents only rarely have hypertension.

Key words; hypertension; lead; cadmium; blood pressure; combined exposure

1. Introduction

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Lead and cadmium are widely dispersed in the environment, and individuals in the general population are increasingly exposed to these heavy metals [1,2]. Workers are often exposed to these metals in their places of employment, but adolescents are mainly exposed from non-occupational sources. Lead can damage the central nervous system, kidneys, cardiovascular system, reproductive organs, and hematological system. The main environmental sources of lead are leaded gasoline, lead paint (including lead paint-contaminated dust and soil), water from lead pipes, and industrial emissions [3]. Lead exposure also occurs through cigarette smoking or consumption of certain foods [4,5]. Thus, lead enters the body via inhalation or ingestion [6]. A recent systematic review concluded that long-term exposure to high levels of lead can lead to hypertension in adults [7], and a previous meta-analysis reported that a two-fold increase in blood lead concentration was associated with a 1.0-mmHg increase in systolic blood pressure (SBP) and a 0.6-mmHg increase in diastolic blood pressure (DBP) [8]. A more recent metaanalysis by Nawrot et al. [9] confirmed the statistically significant relationship between elevated blood lead and increased BP. Our previous studies showed that blood lead level was associated with increased BP and risk of hypertension in the general adult population of Korea [10]. However, previous studies of the relationship of blood lead level with BP in adolescents and children have had inconsistent results [11-17].

Cumulative exposure to cadmium can also increase the risk for overall mortality, as well as cardiovascular, neurological, renal, and developmental diseases [1]. Environmental cadmium is ubiquitous in air, soil, and water due to industrial activities, use of phosphate fertilizers, combustion of motor fuels, and release of particles from tire wear [1,18,19]. Cadmium has a biological half-life of more than 10 years in the whole body, and body levels increase with age because only a minute part of the body burden (0.01–0.02%) is excreted each day [1]. In

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nonsmokers, diet is the major source of cadmium exposure; in smokers, tobacco is the major source because tobacco plants, like other plants, take up cadmium [20]. Animal studies [21-24], occupational studies [25], and general population studies in adults [8,10,26-31] have reported associations between hypertension and blood cadmium level. However, no previous studies have reported the relationship of blood cadmium level with BP in adolescents and children.

The present study evaluated the association of BP with blood levels of cadmium, lead, and cadmium and lead together (lead+cadmium) in a representative sample of adolescents (age 10-18 years) from Korea by use of 2010-2016 data from the Korean National Health and Nutrition Examination Survey (KNHANES).

2. Methods

2.1 Design and data collection

This study used data from the Korea National Health and Nutrition Examination Survey (KNHANES) of 2010–2016, which included KNHANES V (2010-2012), KNHANES VI (2013), and KNHANES VII (2016). These surveys were conducted annually by use of a rolling sample design that employs a complex, stratified, multistage probability cluster analysis of a representative sample of the non-institutionalized civilian population in South Korea. Thus, the KNHANES is a large representative population study with rigorous quality controls. These surveys are performed by the Korean Centers for Disease Control and Prevention, and the Korean Ministry of Health and Welfare, and have three components: a health interview, a health examination, and a nutrition survey. This survey was approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention (approval nos. 2008-04EXP-01-C, 2009-01CON-03-2C, and 2010-02CON-21-C).

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The present cross-sectional analysis examined subjects aged 10-18 years-old who completed the health examination survey, which included measurement of blood metals, and the nutrition survey [32]. The final analytical sample consisted of 1776 adolescents (age 10-18 years, 917 males and 859 females). Kim [33] provided details on the design of the survey. Briefly, information on age, education, smoking history, and alcohol intake was collected during the health interview. Height and weight were recorded with the participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). Based on BMI, subjects were classified as lean (BMI < 18.5 kg/m^2), normal (18.5 ≤ BMI < 25 kg/m^2), or obese (BMI ≥ 25 kg/m^2). Age at the time of the interview was determined for categorization into three age groups (10-12 years-old, 13-15 years-old, and 16-18 years-old). Area of residence was categorized as urban (within an administrative division of a city) or rural (outside the administrative division of a city). Nonsmokers were those who said they had never smoked tobacco, and all others as smokers. Nondrinkers were those who said they never drank alcohol, and all others as drinkers. Data on alcohol and tobacco consumption were collected confidentially, so that parents did not know the answers. Regular walking was defined as indoor or outdoor walking for at least 30 min at a time, at least 3 times per week. Regular exercise was defined as exercising at least 5 times per week (≥30 min per session) in moderate activities (swimming slowly, playing doubles tennis or volleyball, or performing occupational or recreational activities while carrying light objects), or exercising at least 3 times per week (≥20 min per session) in vigorous activities (running, climbing, cycling fast, swimming fast, football, basketball, squash or singles tennis, jumping rope, or performing occupational or recreational activities while carrying heavy objects).

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2.2. Measurement of blood pressure

BP was measured while subjects were seated following a 5 min rest period, and the reported value is the average of 3 measurements with a mercury sphygmomanometer on the right arm [34]. Hypertension was defined by a DBP of at least 90 mmHg or a SBP of at least 140 mmHg. None of the adolescent subjects reported current use of an antihypertensive medication. Prehypertension was defined by a DBP of at least 80 mmHg (but below 90 mmHg), or a SBP of at least 120 mmHg (but below 140 mmHg). Prehypertension was treated as a dichotomous variable, and DBP and SBP as continuous variables.

2.3. Measurement of creatinine and hemoglobin

Serum creatinine was measured by the kinetic Jaffe method using an autoanalyzer (model 7600; Hitachi, Tokyo, Japan). Blood hemoglobin was measured with an XE-2100D Hematology Analyzer (Sysmex, Tokyo, Japan).

2.4 Measurement of lead and cadmium in whole blood

To measure blood lead and cadmium levels, 3-mL samples were drawn into BD vacutainer tubes containing EDTA for trace-element determination (K2 EDTA tube, Vacutainers®). Lead and cadmium were measured by graphite furnace atomic absorption spectrometry with Zeeman background correction (Perkin Elmer AAnalyst 600, Perkin Elmer, Turku, Finland).

Analysis of all blood metals was performed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare. For internal quality assurance and control, commercial reference materials were used (Lyphochek® Whole Blood Metals Control, Bio-Rad, Hercules, CA, USA); the coefficients of variation were 2.65% to 6.50% (lead) and 0.95% to 4.82% (cadmium). As part of external quality assurance and control, this institute

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passed 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 was also certified by the Ministry of Labor as one of the designated laboratories for analysis of specific chemicals, including heavy metals and certain organic chemicals. The method detection limits were 0.207 μg/dL for lead and 0.081 μg/L for cadmium. All samples were above these detection limits.

2.5 Statistical analysis

Statistical analyses were performed using SAS (Version 9.4, SAS Institute, Cary, NC, USA) and SUDAAN (Release 11.0, Research Triangle Institute, Research Triangle Park, NC, USA), a software package that incorporates sample weights and adjusts analyses for complex sample design. Survey sample weights were used in all analyses to produce estimates that were representative of the non-institutionalized civilian population of Korea.

The levels of blood lead and cadmium were $\log_2$-transformed because their distributions were positively skewed. Adjusted geometric means (GMs) and 95% confidence intervals (CIs) are reported according to sex, age group, residence area, smoking status, drinking status, hypertensive status, and year of examination by using the Proc Regress function in SUDAAN.

To estimate the adjusted mean differences in DBP and SBP associated with doubling of blood lead and cadmium levels, the BP was regressed against $\log_2$-transformed blood metal concentration, with adjustment of covariates. Quartiles of blood lead and cadmium levels were also used as independent variables to examine their association with BP in multiple regression analysis (with covariate adjustment). The covariates were sex, age, residence area, smoking status, drinking status, BMI, year of measurement, physical activities, hemoglobin, and serum creatinine. Next, odds ratios (ORs) and 95% CIs for pre-hypertension ($90 > \text{DBP} \geq 80$ mmHg or

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158 140 > SBP ≥ 120 mmHg) were calculated for $\log_2$-transformed blood lead and cadmium levels
159 and for quartiles of the two metals after adjustment of the same covariates as in the logistic
160 regression analyses. The association of the combined level of blood lead and cadmium
161 (lead+cadmium) with BP was assessed by creating 2 categorical variables: lowest quartile of
162 lead+cadmium and highest quartile of lead+cadmium. Then, multiple logistic regression analysis
163 was performed to investigate the association of the lead+cadmium level with the risk of pre-
164 hypertension.
165
166 **3. Results**
167 Table 1 shows the adjusted GMs and 95% CIs of blood levels of lead and cadmium of
168 subjects in different categories. The overall GM of blood lead was 1.192 μg/dL and that of blood
169 cadmium was 0.317 μg/L. Males had a higher blood lead level (1.308 μg/dL *vs.* 1.073 μg/dL),
170 but there was no sex difference in blood cadmium level (0.322 μg/L *vs.* 0.311 μg/L). There was a
171 trend of decreasing blood lead level during the study period, and blood cadmium level in 2010
172 was higher than in all other years. Blood lead level declined with increasing age, whereas blood
173 cadmium level increased with increasing age. There was no significant difference in the blood
174 metal level of adolescents living in rural and urban areas. The blood lead and cadmium levels
175 were unrelated to performance of regular exercise or regular walking. The blood lead and
176 cadmium levels were greater in smokers than non-smokers, but alcohol consumption had no
177 effect. The prehypertensive and normotensive groups had similar mean levels of blood lead and
178 cadmium.
179 Table 2 shows the relationships of different variables with BP in the adolescent study
180 subjects. Males, older individuals, and those in the highest quartile of lead+cadmium were more

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likely to have high SBP. Subjects in the third quartile of lead or cadmium were more likely to have low DBP.

We regressed DBP and SBP against $\log_2$-transformed blood lead concentration (a continuous independent variable), with adjustment for covariates, to estimate adjusted mean differences in DBP and SBP associated with a doubling of blood lead (Table 3). We also performed multiple regression analysis, with adjustment for covariates, to assess the association of blood lead quartiles and blood cadmium quartiles with BP. The results indicate no significant association of blood lead level or blood cadmium level with SBP or DBP.

We also calculated the ORs and 95% CIs for prehypertension for blood lead and cadmium levels and their quartiles (Table 4). As above, the results indicate no association of blood lead level or blood cadmium level with the risk of prehypertension. A logistic regression analysis that used quartiles of blood metals as an independent variable indicated no association with the risk of prehypertension. There were no associations of metal levels with the risk for prehypertension after adjustment for blood lead or cadmium.

Logistic regression analysis comparing subjects in the highest and lowest quartiles of blood lead+cadmium level, with covariate adjustment, indicated a significant risk for prehypertension for those in the highest quartile (Table 5; OR = 3.232, 95% CI = 1.078–9.682).

4. Discussion

The overall GM blood lead level was 1.192 μg/dL in our adolescent subjects. This is higher than reported in the recent U.S. National Health and Nutrition Examination Survey (NHANES) for those aged 12-19 years-old (0.680 μg/dL in 2009-2010 and 0.554 μg/dL in 2011-2012) [35]. The different environments of Korea and the U.S. may explain these differences.

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Previous studies have also reported higher blood lead levels in males than females [35-38]. In recent years, exposure to lead has decreased substantially in South Korea, mostly due to public health measures. Korea began to phase out leaded gasoline in 1986, and blood lead levels have declined steadily since then [39], with a more rapid decline in the early 2000s [36,40]. The present study also indicated that blood lead levels declined in Korean adolescents from 2010 to 2016.

The overall GM blood cadmium level was 0.317 μg/L in our adolescent subjects. The blood cadmium level was not reported for those aged 12-19 years in the U.S. NHANES study, because many of the results were below the limit of detection; however, it is likely that our subjects had higher blood cadmium levels that U.S. adolescents because Korean adults have higher blood levels of cadmium than U.S. adults [35]. Previous studies have reported higher blood cadmium levels in female adults than male adults [32,41,42], but we found no sex differences in Korean adolescents. Our findings that older adolescents and smokers had higher blood cadmium levels are consistent with previous reports [36-38]. Moon *et al.* [43] studied the general population of South Korea and found that diet was the main source of cadmium exposure, but cigarette smoking is also a well-known source of cadmium exposure [44]. Several previous studies of Asian populations found that blood cadmium levels were higher in subjects from northeastern Asia (Korea, Japan, and China) than in Western countries, possibly because of the lower consumption of rice in the West [45-48]. Thus, additional environmental protection measures and education on maintaining a healthy lifestyle are needed so the Korean general population is protected from further exposure to this heavy metal.

Importantly, our analysis showed that an elevated level of lead or cadmium was not significantly associated with increased BP or prehypertension in Korean adolescents. However,

227 an elevated level of cadmium+lead was significantly associated with prehypertension in these
228 study subjects.

229 A high blood lead body level is well known to be associated with hypertension in adults
230 [7], but few studies have evaluated its effects on BP in adolescents. One study reported that
231 young adults with high childhood blood lead levels had higher bone lead and 3-4 mmHg higher
232 SBP and DBP [11]. The Oswego Children's Study reported that umbilical cord blood lead level
233 was positively associated with higher BP at age 9.5 years, and that early-childhood blood lead
234 (mean age, 2.6 years) was associated with increased BP in response to acute stress tasks at 9.5
235 years of age, particularly in children with low socioeconomic status [12,13]. Other studies of
236 blood lead in children found it had no effect on BP [15-17]. The onset of a cardiovascular or
237 other disease in adulthood due to lead exposure in childhood has not been sufficiently studied
238 [49].

239 Previous studies demonstrated that elevated blood cadmium level is associated with
240 hypertension in adults [8,10,26-31], but there have been no such clinical or epidemiological
241 studies of children or adolescents [50].

242 To our best knowledge, the present study is the first to identify an association of
243 prehypertension with the combined level of blood lead and cadmium in adolescents. Our
244 previous study of Korean adults showed that the combined level of lead and cadmium had a
245 stronger association with BP than exposure to either individual metal [9]. We suggest two
246 reasons for this difference between adults and adolescents. First, adolescents have lower blood
247 levels of these heavy metals because they do not work in environments where they are common
248 contaminants. Second, hypertension is much rarer in adolescents than adults. Thus, the
249 association of cadmium alone and lead alone with blood pressure were not significant, but an

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elevated combined level of cadmium and lead was associated with prehypertension.

Previous *in vivo* and *in vitro* studies have shown that chronic exposure to lead causes hypertension and cardiovascular disease by promoting oxidative stress and limiting nitric oxide availability [51]. General population studies have reported inverse associations between estimated glomerular filtration rate and blood lead levels below 5 μg/dL [52], and this impaired renal function could lead to hypertension.

The biological mechanisms responsible for the association of blood cadmium level with increased BP and hypertension are uncertain. It is possible that the well-established nephrotoxic effects of cadmium explain this effect [26,27,53]. In particular, the glomerular membrane filters the cadmium-metallothionein complex, which is then transported from the blood to the renal tubular cells [54,55]. In renal cells, the cadmium-metallothionein complex enters the lysosomes, which release cadmium into the cytosol and degrade metallothionein. Cadmium that is not bound to metallothionein can injure the renal tubules [56], and lead to salt retention, volume overload, and eventually hypertension [53]. This cadmium-induced kidney toxicity can proceed concurrently with renal tubular and glomerular damage, even at low cadmium concentrations [57]. However, our data indicated no association of blood cadmium level with nephrotoxicity. Cadmium can also cause inflammation and facilitate atherosclerosis, also have vascular effects [58,59].

The present findings, which indicate that the combined blood level of lead and cadmium is associated with the risk of prehypertension of Korean adolescents, have important public health implications. In particular, our results suggest that public health policies should consider the effect of combined exposures, which may be frequently observed, in adolescents. This study also had some limitations. First, our results are based on cross-sectional analysis, similar to many

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273 previous reports. Therefore, we did not identify temporal relationships and cannot establish
274 causality of the reported associations because there may be unidentified intermediary factors.
275 Second, the KNHANES does not consider urinary cadmium (half-life of 15–30 years) as a
276 biomarker of lifetime exposure to cadmium [60,61]; instead, it considers blood cadmium (half-
277 life of 3–4 months) as the most valid biomarker for recent cadmium exposure [44,62]. Finally,
278 the blood lead concentrations reported here indicate recent exposure, and do not reflect the total
279 body burden over the subjects' lifetimes. Further studies of bone lead with X-ray fluorescence,
280 which indicates long-term cumulative exposures, are needed [2]. The strengths of this study are
281 that we used a representative sample of the general adolescent population of South Korea, we
282 applied rigorous quality controls to the procedures used in the KNHANES, and we adjusted for
283 most potential confounders and effect modifiers (sex, age, residence area, smoking and drinking
284 status, BMI, physical activity, hemoglobin, serum creatinine, and concurrent exposure to other
285 heavy metals).

286 In conclusion, our study of adolescents in Korea showed that the combined level of
287 blood lead and cadmium is associated with increased risk of prehypertension.

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Table 1. Means and 95% confidence intervals (Cls) of blood lead and cadmium of adolescent by classification variables according to KNHANES 2010-2016

Classification		No	Mean (95% Confidence interval)¶	
			Blood lead (μg/dL)	Blood cadmium (μg/dL)
All		1776	1.192 (1.165~1.219)	0.317 (0.306~0.328)
Sex	Male	917	1.308 (1.268~1.348)	0.322 (0.307~0.337)
	Female	859	1.073 (1.037~1.111)**	0.311 (0.296~0.328)
Year	2010	365	1.418 (1.348~1.493)	0.383 (0.350~0.420)
	2011	381	1.285 (1.224~1.349)**	0.333 (0.309~0.359)*
	2012	364	1.153 (1.093~1.217)**	0.302 (0.280~0.325)**
	2013	360	1.192 (1.129~1.259)**	0.238 (0.217~0.261)**
	2016	306	1.001 (0.912~1.098)**	0.337 (0.304~0.374)
Age group	10-12	562	1.349 (1.287~1.413)	0.270 (0.252~0.290)
	13-15	639	1.178 (1.139~1.218)**	0.330 (0.314~0.348)**
	16-18	575	1.099 (1.052~1.148)**	0.342 (0.321~0.365)**
Residence area	Urban	1495	1.182 (1.154~1.209)	0.319 (0.307~0.331)
	Rural	281	1.248 (1.182~1.319)	0.307 (0.282~0.333)
Exercise	Yes	218	1.270 (1.154~1.399)	0.288 (0.258~0.322)
	No	1558	1.175 (1.143~1.208)	0.324 (0.312~0.337)
Walk	Yes	218	1.186 (1.092~1.288)	0.325 (0.296~0.357)
	No	1558	1.193 (1.161~1.226)	0.315 (0.303~0.328)
Smoking status	No	1623	1.181 (1.153~1.210)	0.304 (0.294~0.315)
	Yes	153	1.295 (1.208~1.389)*	0.464 (0.405~0.531)**
Drinking status	No	1441	1.181 (1.151~1.211)	0.311 (0.300~0.322)
	Yes	335	1.233 (1.167~1.302)	0.340 (0.311~0.371)
Prehypertension	No	1740	1.192 (1.166~1.218)	0.317 (0.307~0.328)
	Yes	36	1.183 (1.044~1.341)	0.312 (0.251~0.388)

¶: adjusted for all classification variables except its own variable. *:p<0.05, **:p<0.01

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Table 2. Means and 95% confidence intervals (Cls) of diastolic and systolic blood pressure of adolescent by classification variables according to KNHANES 2010-2016

Classification		Mean (95% Confidence Interval)¶	
		Diastolic blood pressure (mmHg)	Siastolic blood pressure (mmHg)
Sex	Male (N=917)	66.0 (65.3~66.7)	109.7 (108.9~110.4)
	Female (N=859)	66.9 (66.1~67.7)	105.8 (105.0~106.7)**
Year	2010	66.5 (65.1~67.9)	107.0 (105.6~108.4)
	2011	65.2 (64.0~66.3)	106.9 (105.6~108.1)
	2012	66.3 (64.7~67.9)	108.3 (106.8~109.8)
	2013	65.4 (64.2~66.5)	108.0 (106.7~109.3)
	2016	68.2 (65.9~70.6)	108.9 (106.7~111.2)
Age group	10-12	64.1 (63.0~65.2)	106.6 (105.4~107.8)
	13-15	66.4 (65.6~67.3)	107.8 (106.9~108.7)
	16-18	68.1 (67.1~69.0)	108.9 (107.8~109.9)*
Residence area	Urban	66.5 (65.9~67.0)	107.7 (107.2~108.3)
	Rural	66.1 (64.9~67.3)	108.5 (107.1~109.9)
Exercise	Yes	64.7 (62.7~66.7)	106.9 (104.8~109.0)
	No	66.8 (66.1~67.5)	108.1 (107.4~108.8)
Walk	Yes	66.1 (64.0~68.1)	109.0 (106.9~111.1)
	No	66.5 (65.8~67.1)	107.6 (106.9~108.3)
Smoking status	No	66.6 (66.1~67.1)	108.0 (107.4~108.5)
	Yes	64.6 (62.6~66.5)	106.9 (105.0~108.9)
Drinking status	No	66.5 (65.9~67.0)	107.9 (107.3~108.5)
	Yes	66.2 (65.1~67.3)	107.7 (106.4~108.9)
Blood Lead Quartile	1st Q	66.9 (66.0~67.8)	108.3 (107.3~109.3)
	2nd Q	67.0 (66.0~68.0)	108.0 (106.9~109.0)
	3rd Q	65.5 (64.5~66.5)*	107.4 (106.4~108.4)
	4th Q	66.3 (65.4~67.3)	107.8 (106.7~108.9)
Blood Cadmium Quartile	1st Q	67.0 (66.0~68.0)	107.8 (106.8~108.8)
	2nd Q	66.2 (65.4~67.0)	107.5 (106.5~108.5)
	3rd Q	65.1 (64.2~66.1)**	107.5 (106.5~108.5)
	4th Q	67.3 (66.2~68.3)	108.7 (107.5~109.9)
Combined PbB & CdB	Lowest Q	67.5 (65.8~69.2)	106.6 (104.8~108.4)

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		Highest Q		68.5 (66.7~70.2)		110.0 (107.9~112.1)*	

¶: adjusted for all classification variables except its own variable. *:p<0.05, **:p<0.01

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Table 3. Differences (95% confidence intervals (Cls)) in diastolic and systolic blood pressure by blood lead (PbB) and cadmium (CdB) level (continuous and quartile values) after covariate adjustment#

Classification		PbB only	PbB & CdB			CdB only	PbB & CdB
Model 1: Diastolic blood pressure							
Per doubling of PbB (μg/dL)¶		-0.680 (-1.581~0.221)	-0.696 (-1601~0.209)	Per doubling of CdB (μg/dL)¶		-0.015 (-0.607~0.576)	0.062 (-0.533~0.658)
PbB Quartile	1st Q	0 (Reference)		CdB Quartile	1st Q	0 (Reference)	0 (Reference)
	2nd Q	0.065 (-2.238~1.385)	0.0805 (-1.235~1.396)		2nd Q	-0.924 (-0.924~0.388)	-0.845 (-2.142~0.451)
	3rd Q	-1.411 (-3.33~-0.017)	-1.406 (-2.784~-0.02)		3rd Q	-1.948 (-1.948~-0.566)	-1.880 (-3.246~-0.513)
	4th Q	-0.511 (-1.363~0.844)	-0.582 (-1.915~0.751)		4th Q	0.101 (0.101~1.565)	0.232 (-1.221~1.686)
Model 2: Systolic blood pressure							
Per doubling of PbB (μg/dL)¶		-0.099 (-1.098~0.898)	-0.222 (-0.228~0.785)	Per doubling of CdB (μg/dL)¶		0.445 (-0.178~1.068)	0.471 (-0.161~1.101)
PbB Quartile	1st Q	0 (Reference)		CdB Quartile	1st Q	0 (Reference)	0 (Reference)
	2nd Q	-0.255 (-1.755~1.223)	-0.301 (-1.787~1.184)		2nd Q	-0.346 (-1.755~1.062)	-0.305 (-1.719~1.107)
	3rd Q	-0.788 (-1.773~0.651)	-0.859 (-2.303~0.583)		3rd Q	-0.327 (-1.773~1.119)	-0.281 (-1.744~1.181)
	4th Q	-0.304 (-0.682~1.218)	-0.470 (-1.983~1.041)		4th Q	0.883 (-0.682~2.449)	0.964 (-0.609~2.537)

#: adjusted for sex, year, age, residence area, smoking and drinking status, physical activities, serum creatinine, BMI, and hemoglobin

¶: Mean differences in systolic and diastolic pressure with doubling of the blood lead levels

Blood lead quartile: <1.07, 1.07-1.341, 1.342-1.655, >1.655 μg/dL for male, <0.839, 0.839-1.076, 1.077-1.371, >1.371 μg/dL for female

Blood cadmium quartile: <0.223, 0.223-0.319, 0.320-0.451, >0.451 μg/dL for male, <0.225, 0.225-0.310, 0.311-0.440, >0.441 μg/dL for female

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Table 4. Odd ratios (95% CI) for having pre-hypertension by blood lead (PbB) and cadmium (CdB) level (continuous and quartile values) after covariate adjustment#

Classification		PbB only	PbB & CdB			CdB only	PbB & CdB
Per doubling of PbB (μg/dL)¶		0.906 (0.629~1.305)	0.883 (0.613~1.271)	Per doubling of CdB (μg/dL)¶		1.091 (0.896~1.327)	1.105 (0.909~1.344)
PbB Quartile	1st Q	(Reference)	(Reference)	CdB Quartile	1st Q	(Reference)	(Reference)
	2nd Q	0.943 (0.589~1.509)	0.935 (0.583~1.500)		2nd Q	1.034 (0.633~1.69)	1.047 (0.644~1.703)
	3rd Q	0.797 (0.495~1.282)	0.777 (0.481~1.253)		3rd Q	0.957 (0.581~1.577)	0.968 (0.587~1.598)
	4th Q	1.002 (0.598~1.678)	0.950 (0.567~1.592)		4th Q	1.342 (0.850~2.117)	1.360 (0.866~2.133)

#: adjusted for sex, year, age, residence area, smoking and drinking status, physical activities, serum creatinine, BMI, and hemoglobin

¶: Odd ratios (95% CI) for having hypertension with doubling of the blood cadmium levels

Blood lead quartile: <1.07, 1.07-1.341, 1.342-1.655, >1.655 μg/dL for male, <0.839, 0.839-1.076, 1.077-1.371, >1.371 μg/dL for female

Blood cadmium quartile: <0.223, 0.223-0.319, 0.320-0.451, >0.451 μg/dL for male, <0.225, 0.225-0.310, 0.311-0.440, >0.441 μg/dL for female

Table 5. Odd ratios(95% CI) for having pre-hypertension by low and high sub group of combined PbB and CdB after covariate adjustment#

Classification		Pre-hypertension
Combined PbB & CdB	Both 1st Q	0 (Reference)
	Both 4th Q	3.232 (1.078~9.682)

#: adjusted for sex, year, age, residence area, smoking and drinking status, physical activities, serum creatinine, BMI, and hemoglobin