

ORIGINAL ARTICLE

Does low lead exposure affect blood pressure and hypertension?

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Abstract

Objectives: Historically, little was known about the effects of low blood lead level (BLL < 10 µg/dL) on hypertension (HTN). The purpose of this study was to assess the effects of low BLL on blood pressure (BP) and HTN in lead-exposed male workers in the Republic of Korea.

Methods: From the year 2000 to 2004, 12,060 male workers underwent an Annual Specialised Medical Check-up for lead; 7,341 subjects had a peak BLL < 10 µg/dL and were selected for the study. The quartiles of peak BLL in lead-exposed workers were as follows: first (0.01-3.68 µg/dL), second (3.69-5.19 µg/dL), third (5.20-6.86 µg/dL), and fourth (6.87-10.00 µg/dL). To examine the relationship between BLL and pre-HTN (systolic BP [SBP] ≥ 120-140 mmHg; diastolic BP [DBP] ≥ 80-90 mmHg) and between BLL and HTN (SBP ≥ 140 mmHg; DBP ≥ 90 mmHg), the quartiles of BLL were used as independent variables in multiple logistic regression analysis.

Results: In multiple linear regression analyses, SBP (β 0.04, $P < .01$) and DBP (β 0.06, $P < .01$) increased in line with a 1 µg/dL increase in BLL. The odds ratio (OR) of HTN in the fourth versus first BLL quartile (1.54; 95% confidence interval [CI]: 1.26, 1.89) was statistically significant.

Conclusion: SBP and DBP were statistically significantly associated with peak BLL. A BLL ≥ 6.87 µg/dL was associated with HTN; thus, even in workers with low BLLs (<10 µg/dL), management of BP is likely to be necessary. Modulation of the current safety standards for BLLs in workers will be needed.

KEYWORDS

blood pressure, hypertension, lead

1 | INTRODUCTION

Hypertension (HTN) is a serious health problem that affects approximately one billion people worldwide today.¹ In the Republic of Korea, more than 11 million Korean adults are estimated to have HTN.² The causes of HTN can be divided into genetic and environmental factors. Known environmental

factors to date include lifestyle habits such as smoking, drinking and diet, stress, and exposure to harmful heavy metals including cadmium, mercury, and lead.^{3,4}

Among heavy metals, lead has been suspected to influence blood pressure (BP) and cardiovascular disease for many years.⁵ Population research on the cardiovascular effects of lead has focused largely on the association with

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BP or HTN.⁶ In the second National Health and Nutrition Examination Survey in the United States, a direct relationship was found between blood lead level (BLL) and systolic BP (SBP) and diastolic BP (DBP) in men and women.⁷ In the 2008-2013 Korean National Health and Nutrition Examination Survey, an association was found between BLL and the risk of HTN in the general population in Korea.⁸

A systematic review concluded that long-term exposure to high levels of lead can cause HTN.⁶ Some studies also demonstrated a progressive dose-response relationship between lead exposure and BP.⁶ However, the shape of the dose-response relationship has not been completely characterised, particularly at low levels of exposure.⁶ The question of whether low-level lead exposure increases BP in the population is still controversial. In 1991, the US Centers for Disease Control and Prevention (CDC) established 10 µg/dL as the lowest level of concern for BLLs in children.⁹ This value is extremely important because, historically, policy makers and public health officials typically acted to remove sources of lead exposure only after the CDC's level of concern had been exceeded.¹⁰ However, the lowest BLL associated with BP in adults remains unclear, although available studies suggest no evidence of a threshold effect.⁶

Since 1972, lead-exposed workers in the Republic of Korea have been required to undergo an Annual Specialised Medical Check-up (ASMC) under the Industrial Health Safety Act.¹¹ Using ASMC data, we aimed to retrospectively analyze the potential association of BLL (<10 µg/dL) with BP and HTN.

2 | METHODS

2.1 | Study subjects

Since 2000, ASMC data for exposure to occupational hazards (143 chemicals, 6 types of dust, 8 physical agents, and 19 metals, including lead) have been electronically stored and monitored by the Korean Occupational Safety and Health Agency (KOSHA). The ASMC is conducted at more than 100 medical centers nationwide approved by KOSHA for the evaluation of Korean workers exposed to lead in the form of dust, fumes, etc.^{11,12} From 2000 to 2004, all study subjects underwent more than one General Health Check-up (GHC). The GHC is available to all local householders aged >20 years, including individuals covered by workplace health insurance. For blue-collar workers, the GHC is required annually and comprises routine questions about medical history, a physical examination, and laboratory tests. The physical examination comprises measurement of the subject's height, weight, SBP, DBP, etc. Laboratory tests comprise an evaluation of overnight

fasting blood sugar, lipid profile, total cholesterol (TC), etc.¹³ A total of 12 060 male workers underwent at least one ASMC for lead, excepting tests for other heavy metals and noise, from January 1, 2000 to December 31, 2004. The ASMC data for these workers were merged into the GHC data during the same period. Among these workers, 7341 (60.9%) with no missing values for mean SBP, DBP, Body Mass Index (BMI), and TC, and whose mean peak BLL was <10 µg/dL during the study period were selected as study subjects.

2.2 | Sampling and analysis of blood lead levels

KOSHA conducts a twice-yearly quality assurance program to monitor the institutes and hospitals that participate in the ASMC.^{12,14} These institutes and hospitals should pass an analytical proficiency test for trace metal analysis to continue participating in the ASMC program.^{12,14} KOSHA-Licensed institutes and hospitals collect and analyze blood samples from lead workers as required by the ASMC. Sampling and analysis of BLL are performed in accordance with the South Korean Occupational Safety and Health Administration (KOSHA)-CODE H-09-1998,^{14,15} which was developed by KOSHA based on guidelines established by the National Institute for Occupational Safety and Health.^{14,16}

2.3 | Measurement of BP, TC, and BMI

The BPs of the examinees were measured after a sufficient rest period before the examination.¹³ BP was measured using an automatic sphygmomanometer after the subject had maintained 5 minutes of stable condition while sitting.¹³ If SBP was ≥120 mmHg or DBP was ≥80 mmHg in the first examination, re-examination was performed after more than 2 minutes.¹³ If SBP was ≥140 mmHg or DBP was ≥90 mmHg in the first examination, a second examination was performed after 2 weeks. The second examination was performed in the same manner as the first.¹³ HTN was defined as a mean DBP of at least 90 mmHg or a mean SBP of at least 140 mmHg from January 1, 2000 to December 31, 2004. Pre-HTN was defined as a mean DBP of at least 80 mmHg (but below 90 mmHg) or a mean SBP of at least 120 mmHg (but below 140 mmHg) during this period.⁸ The authors could not consider the use of anti HTN drugs in workers to distinguish between normal BP and HTN due to the lack of data. The TC test was performed after fasting for more than 8 hours and TC and BMI (kg/m²) were measured in accordance with the guidelines of the Ministry of Employment and Labor.¹³ The mean TC and BMI during the study period were used.

2.4 | Study ethics

The study protocol was reviewed and approved by the institutional review board of Dongguk University Gyeongju Hospital. Informed Consent Registry and the Registration No. of the study/Trial: 110757-201602-HR-06-02 (This study met the requirements for exemption from IRB review, which included obtaining informed consent from the subjects).

2.5 | Statistical analyses

To assess the differences in pre-HTN, HTN, SBP, DBP, subjects' age in the year 2000, TC, and BMI with peak BLL

quartile, one-way analysis of variance and the chi-squared test were used. To examine the demographics of lead-exposed male workers, the *t* test was used (Table 1). To examine the association between BP and BLL (per $\mu\text{g}/\text{dL}$), SBP and DBP for study subjects were regressed against BLLs after adjustment for covariates (Table 2). Odds ratios (ORs) and 95% confidence intervals (CIs) for pre-HTN and HTN were calculated for the quartiles of BLL: first (0.01-3.69 $\mu\text{g}/\text{dL}$), second (3.70-5.19 $\mu\text{g}/\text{dL}$), third (5.20-6.86 $\mu\text{g}/\text{dL}$), and fourth (6.87-10.00 $\mu\text{g}/\text{dL}$; Table 3). The covariates were the same for multiple linear regression and logistic regression analyses (age in the year 2000, TC, BMI), which were performed using the R Studio program (version 3.5.2). HTN and pre-HTN were treated as dichotomous variables, with DBP and SBP as continuous variables.

TABLE 1 Demographic of male lead exposed workers (n = 7,341) in South Korea

Variables	n (%) or mean \pm SD
Age in 2000 (y)	
<20	373 (5.1)
20-30	3,493 (47.6)
30-40	2,271 (30.9)
40-50	975 (13.3)
>50	29 (3.1)
Age in 2000 (y)	31.1 \pm 0.8.5
Blood pressure	
Normal	2,489 (33.9)
Prehypertension	3,950 (53.8)
Hypertension	902 (12.3)
Systolic blood pressure (mmHg)	121.4 \pm 12.6
Diastolic blood pressure (mmHg)	76.5 \pm 9.2
Peaklead ($\mu\text{g}/\text{dL}$)	5.3 \pm 0.2.2
Body mass index	22.6 \pm 0.3.0
Total cholesterol (mg/dL)	177.8 \pm 34.1

TABLE 2 Characteristics of lead-exposed workers in South Korea by quartiles of (Q1-Q4) of lead in blood

Quartile of blood lead level	1st	2nd	3rd	4th	P-value	Total
Range	0.01-3.68	3.69-5.19	5.20-6.86	6.87-10.00		0-10.0
n	1,839	1,849	1,820	1,833		7,341
Blood pressure						
Normal	651 (35.4)	650 (35.2)	625 (34.3)	563 (30.7)	<.01	2,489 (33.9)
Prehypertension	1,010 (54.9)	1,006 (54.4)	963 (52.9)	971 (53.0)	<.01	3,950 (53.8)
Hypertension	178 (9.7%)	193 (10.4)	232 (12.7)	299 (16.3)	<.01	902 (12.3)
Age in 2000	28.9 \pm 7.7	30.3 \pm 0.8.1	32.0 \pm 8.8	33.0 \pm 8.9	<.01	31.0 \pm 8.5
Total cholesterol (mg/dL)	175.7 \pm 32.0	176.5 \pm 32.9	178.9 \pm 37.3	180.1 \pm 33.4	<.01	177.8 \pm 33.9
Body mass index	22.7 \pm 3.0	22.7 \pm 2.9	22.8 \pm 3.0	23.0 \pm 3.0	<.01	22.8 \pm 3.0

3 | RESULTS

3.1 | Demographic of study subjects

The mean age of the study subjects in the year 2000 (n = 7341) was 31.1 \pm 8.5 years and most of them were in their 20s and 30s (78.5%). Their mean SBP was 121.4 \pm 12.6 mmHg, DBP was 76.5 \pm 9.2 mmHg, and peak lead was 5.3 \pm 2.2 $\mu\text{g}/\text{dL}$.

TABLE 3 The beta and differences (95% CIs) in systolic blood pressure and diastolic blood pressure by blood lead quartile in lead exposed workers in South Korea

	B	β	S.E.	t	P-value
SBP ^a					
Per BLL $\mu\text{g}/\text{dL}$ ^a	0.24	0.04	0.09	2.55	.01
DBP ^a					
Per BLL $\mu\text{g}/\text{dL}$ ^a	0.35	0.06	0.06	5.45	<.01

Abbreviations: BLL; blood lead level; DBP, diastolic blood pressure; SBP, systolic blood pressure.

^aAdjusted by age in 2000, total cholesterol, body mass index (all are continuous variables).

Their mean BMI was 22.6 ± 3.0 and TC was 177.8 ± 34.1 mg/dL (Table 1).

3.2 | Characteristics of lead-exposed workers according to BLL quartile (Q1-Q4)

SBP, DBP, subject age in the year 2000, TC, and BMI were statistically significantly different according to the BLL quartile ($P < .01$). The proportions of HTN, age in the year 2000, TC, and BMI increased with the increment of the BLL quartile (Table 2).

3.3 | SBP and DBP in lead-exposed workers according to BLL quartile (Q1-Q4)

In multiple linear regression analyses, SBP (β 0.04, $P = .01$) and DBP (β 0.06, $P < .01$) increased in line with a 1 $\mu\text{g}/\text{dL}$ increase in BLL (Table 3).

3.4 | Pre-HTN and HTN in lead-exposed workers according to BLL quartile (Q1-Q4)

The OR of HTN was statistically significantly higher for the fourth versus the first BLL quartile (OR 1.54; 95% CI: 1.26, 1.89) (Table 4).

4 | DISCUSSION

Most previous studies targeted individuals exposed to high lead levels.^{5,6} Therefore, our study is meaningful in that it assesses

the relationship between occupational exposure to low lead levels and BP. Our study showed that SBP and DBP increased with each 1 $\mu\text{g}/\text{dL}$ increment in BLL, and the OR of HTN increased as the BLL quartile increased. The relationship between SBP, DBP, and BLL was examined with multiple linear and logistic regression analysis. A significant link between BLL, SBP, and DBP was found. In addition, an association between BLL and HTN was observed, supported by statistically significant ORs after adjusting for covariates such as subject age in the year 2000, TC and BMI. These findings are compatible with those of previous studies, which concluded that exposure to lead causes BP elevation.^{5,6} BLL is generally used as an indicator of recent exposure to lead, since the half-life of lead in blood is approximately 1 month;¹⁷ bone lead level reflects cumulative exposure. The peak lead level in our study agreed with that in another study, which concluded that bone lead level was positively associated with increased SBP.^{18,19}

Many researchers have reported a relationship between lead exposure and cardiovascular disease.^{5,6,15} BP elevation due to lead exposure has also been observed in cross-sectional, cohort, and experimental studies.^{5,6,20,21} A systematic review concluded that long-term exposure to high levels of lead can cause HTN.⁶ However, the question of whether low-level lead exposure causes increased BP in the population remains controversial because the causal nature of the correlation has not been proven.^{22,23} The published literature suggests only a weak, positive relationship between BP and BLL.²⁴ A previous meta-analysis indicated that a doubling of BLL was associated with a 1.0-mmHg rise in SBP and a 0.6-mmHg rise in DBP.^{6,24} However, the association was not consistently supported by previous studies of BLL and BP.^{25,26} For instance, one study of environmental lead exposure evaluated the relationship between BLL and BP in local residents living near a copper smelter in the Republic of Korea: no correlation between BLL and BP was observed.²⁶

The precise mechanisms underlying the hypertensive effect of chronic low exposure to environmental lead are unknown.⁶ Conversely, the development of HTN in subjects chronically exposed to high lead levels has been attributed to lead nephropathy.^{6,27,28} An inverse association between estimated glomerular filtration rate and BLL has been observed at BLLs below 5 $\mu\text{g}/\text{dL}$ in the general population.²⁷ Changes in the renin-angiotensin system and malfunctions in sodium handling lead to toxic effects after exposure to low lead concentrations.²⁹ Lead exposure causes oxidative stress, which reduces nitric oxide availability, increases systemic vascular resistance,^{30,31} and alters the activity and production of the hormones that control vascular tone.³²

This study has several limitations. First, data about antihypertensive drug use and a family history of HTN, which could be important confounders, were limited because the secondary data were collected via GHC. However, hypertensive

TABLE 4 The association with blood lead quartiles and prehypertension and hypertension in lead exposed workers in South Korea

	OR	95% CI	P-value
Pre hypertension			
Lead 1st ^a	1		
Lead 2nd ^a	1.01	0.87-1.16	.93
Lead 3th ^a	1.00	0.87-1.16	.97
Lead 4th ^a	1.12	0.97-1.30	.13
Hypertension			
Lead 1st ^a	1		
Lead 2nd ^a	1.04	0.83-1.29	.74
Lead 3rd ^a	1.20	0.97-1.48	.10
Lead 4th ^a	1.54	1.26-1.89	<.01

^aAdjusted by age in 2000, total cholesterol, body mass index (all are continuous variables).

heredity and BP elevations after lead exposure were not significantly related in one study,³¹ in which the authors indicated that a study such as ours would be appropriate. Second, our study lacked lead-exposure data for workers before the formation of the study cohort.

Data about the total burden of lead exposure during a worker's lifetime are generally limited; however, some lead-exposed workers may quit their jobs because of lead-related or renal disease.²¹ Finally, the BP-elevating role of lead could be due to other environmental risk factors such as alcohol intake or smoking habit,³³ social economic status,³⁴ salt and potassium intake, physical activity, and psychosocial stress.³⁵ Indeed, Garndjean et al³⁶ showed a significant relationship between alcohol intake and BLL and BP. In our study, information about alcohol intake and smoking habit was not available due to the limited amount of secondary data collected. Further studies are needed that include lifestyle factors, social economic status, employment type, work duration, family history of HTN, and antihypertensive drug use in employees.

Despite these limitations, our study has some important implications. First, all cohort members occupationally exposed to lead were consistently assessed at least once, so that data for up to 5 years were available to determine the median BP and mean values of BMI, TC, and peak BLL. Many previous studies performed single measurements to evaluate lead exposure,⁶ which may have caused BLL and BP measurement errors. However, the possibility of underestimation was reduced in our study due to continuous measurement of BLL and BP for 5 years. Second, ASMC recipients exposed to other metals, and therefore potential confounders, were excluded so that any relationship between lead exposure and BP could be identified more clearly. Furthermore, the use of special medical check-up data allowed for a large sample size and a large retrospective cohort with occupational exposure to low levels of lead, relative to previous similar studies.

5 | CONCLUSIONS

In conclusion, a BLL >6.87 µg/dL was associated with HTN in Korean men occupationally exposed to lead. Lower levels of lead in blood than the current occupational safety standards were shown to elevate BP in our study. The substantial evidence that chronic lead exposure affects cognitive function and renal function at levels <5 µg/dL indicate that the US Centers for Disease Control and Prevention criterion for elevated blood levels in children (10 µg/dL) is too high for adults.^{6,27,37} Consequently, modulation of the current safety standards established by the Korean Ministry of Employment and Labor and the US Occupational Safety and Health Administration for BLLs in workers (currently established

at 30 µg/dL and 40 µg/dL, respectively) is needed.^{38,39} To establish a new reference BLL, long-term accumulation of data and large-sized samples of workers with low BLLs are required through further study. Furthermore, considering the effects of lead on cardiovascular disease including HTN, regulatory and public health interventions should be developed to prevent and reduce lead exposure. A criterion for elevated blood lead levels in adults needs to be established and screened for in preventive services.⁶ For workers with low BLLs (ie below current biological-exposure indices), additional efforts are needed to decrease lead exposure in the workplace, monitor BP, and prevent serious cardiovascular health problems due to HTN.

DISCLOSURE

Approval of the research protocol: This study was reviewed by the Institutional Review Board (IRB) of Dongguk University of Gyeongju Hospital. *Informed consent:* N/A (This study met the requirements for exemption from IRB review, which included obtaining informed consent from the subjects.). *Animal studies:* Not included. *Registry and the registration no. of the study/trial:* 110757-201602-HR-06-02. *Conflict of interest:* The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

YSA and MGK conceived the study idea; YSA collected the data; MGK and YSA analyzed the data; and MGK and YWK led the writing.

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