

BMJ Open Association between blood lead level and risk of stroke in Korean adults: a cross-sectional study in the Korea National Health and Nutrition Examination Survey 2008–2013

Minkyong Kim, Sang-Moon Yun, Jihyun Jeong, Chulman Jo, Young Ho Koh 

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Division of Brain Diseases, Korea National Institute of Health, Cheongju, South Korea

Correspondence to

Dr Young Ho Koh;
koyoungho122@gmail.com

ABSTRACT

Objectives Although lead is a potential risk factor for cardiovascular diseases such as stroke, research on this association in the Korean population remains limited. Therefore, we aimed to investigate the association between lead level and stroke in Korean adults.

Design A population-based cross-sectional study.

Setting The Korea National Health and Nutrition Examination Survey 2008–2013, which enrolled a representative sample of the Korean population.

Participants We excluded participants younger than 20 years, missing weight data, pregnant or lactating, and missing blood lead and stroke data. A total of 11 510 participants were included in this analysis.

Primary and secondary outcome measurement The participants were classified by blood lead concentration into the low-level ($\leq 2.189 \mu\text{g/dL}$, $n=5756$) and high-level ($> 2.189 \mu\text{g/dL}$, $n=5754$) groups. The main outcome, stroke, was assessed by information from physician diagnosis, prevalence of stroke or treatment for stroke. The ORs and 95% CIs were calculated to evaluate the association between blood lead level and stroke using multivariate logistic regression analysis.

Results Although blood lead level was not significantly associated with stroke (OR: 1.30, 95% CI: 0.66–2.58) in the multivariate-adjusted model, in individuals with hypertension, the high-level group was 2.36-fold higher odds of stroke (OR: 2.36, 95% CI: 1.02–5.44) compared to that in the low-level group. No association was observed in individuals with normotension (OR: 0.42, 95% CI: 0.13–1.38, p for interaction=0.007).

Conclusion The association between blood lead concentration and stroke may be influenced by hypertension status. Our findings suggest the need for closer attention to lead exposure in patients with hypertension.

INTRODUCTION

Stroke is the second cause of death worldwide.¹ The WHO Global Health Estimates reported in 2016 that stroke accounted for 10.2% of total deaths and was the leading cause of death in the past 15 years.^{1,2} Statistics

Strengths and limitations of this study

- This study used data from the Korea National Health and Nutrition Examination Survey, which is nationally representative of the non-institutionalised civilians in Korea.
- The association between blood lead and stroke adjusted for various factors including preceding diseases was investigated.
- A causal relationship between blood lead and stroke not clearly obtained because of the cross-sectional study.
- The possibility of presence of residual confounding factors remains, as the observational study.

Korea reported that mortality caused by stroke was fourth highest among causes of death in 2018.³ Stroke is a leading cause of the functional disorder. Previous studies have reported that the risk of disability increased after stroke.^{4,5} In addition, the risk of disability by stroke was higher than myocardial infarction.⁴ The prevalence of stroke leads to poor quality of life,^{6,7} economic burden from medical expense,⁸ and high burden of disease⁹ and disability.¹⁰ Ultimately, it negatively affects both countries and individuals. Therefore, the primary prevention of stroke, which is a high proportion of first onset¹¹ is important.

Lead is a risk factor for cardiovascular disease such as stroke¹² and is widely distributed in gasoline, paint, air pollution, and soil pollution.^{13,14} The health problems associated with short-term and long-term lead exposure affect the haematological and nervous systems, kidney function and cardiovascular system.^{13,15} The reference value for blood lead level was established at $10 \mu\text{g/dL}$, some agencies, including the Centers for Disease Control and Prevention (CDC), recently

defined $5\mu\text{g}/\text{dL}$ as the reference blood lead level for adults in the USA.^{16,17} According to previous studies, both low and high lead concentrations have negative cardiovascular effects.^{18–23} The cohort study of the National Health and Nutrition Examination Survey (NHANES) showed a dose–response relationship between blood lead level and mortality due to stroke (HR: 2.51, 95% CI: 1.20–5.26, p for trend=0.017).¹⁸ Furthermore, a meta-analysis that pooled estimates of relative risk (RR) reported a 1.63-fold increased risk of stroke in individuals with elevated blood lead levels (RR: 1.63, 95% CI: 1.14–2.34).²⁴ Finally, a cross-sectional study in Korean adults that stratified analysis by sex observed a positive association in women (OR: 1.44, 95% CI: 1.09–1.92), but not in men.²⁵

Until now, few studies have assessed the association between lead and stroke in the Korean population. Preceding diseases such as hypertension, dyslipidaemia and diabetes have been associated with lead^{26–28} and are risk factors for stroke.^{29,30} However, previous studies were not adequately controlled for potential confounding factors such as preceding diseases.²⁵ Therefore, we aimed to investigate the association between blood lead level

and stroke considering the effects of preceding diseases in Korean adults.

METHODS

Study population

This study as a cross-sectional analysis was conducted using data from the Korea National Health and Nutrition Examination Survey (KNHANES), which was a nationally representative data.³¹ The nationwide KNHANES recruited participants from the Korean population. The survey enrolled a representative sample of the non-institutionalised Korean population and was performed using a complex sampling design.

Of the 53 829 individuals who participated in the KNHANES 2008–2013, we excluded those who were (1) younger than 20 years ($N=13\,501$), (2) missing weight data ($N=28\,400$), (3) pregnant or lactating ($N=178$) and (4) missing blood lead and stroke data ($N=240$). Finally, we included 11 510 participants in the present study (figure 1).

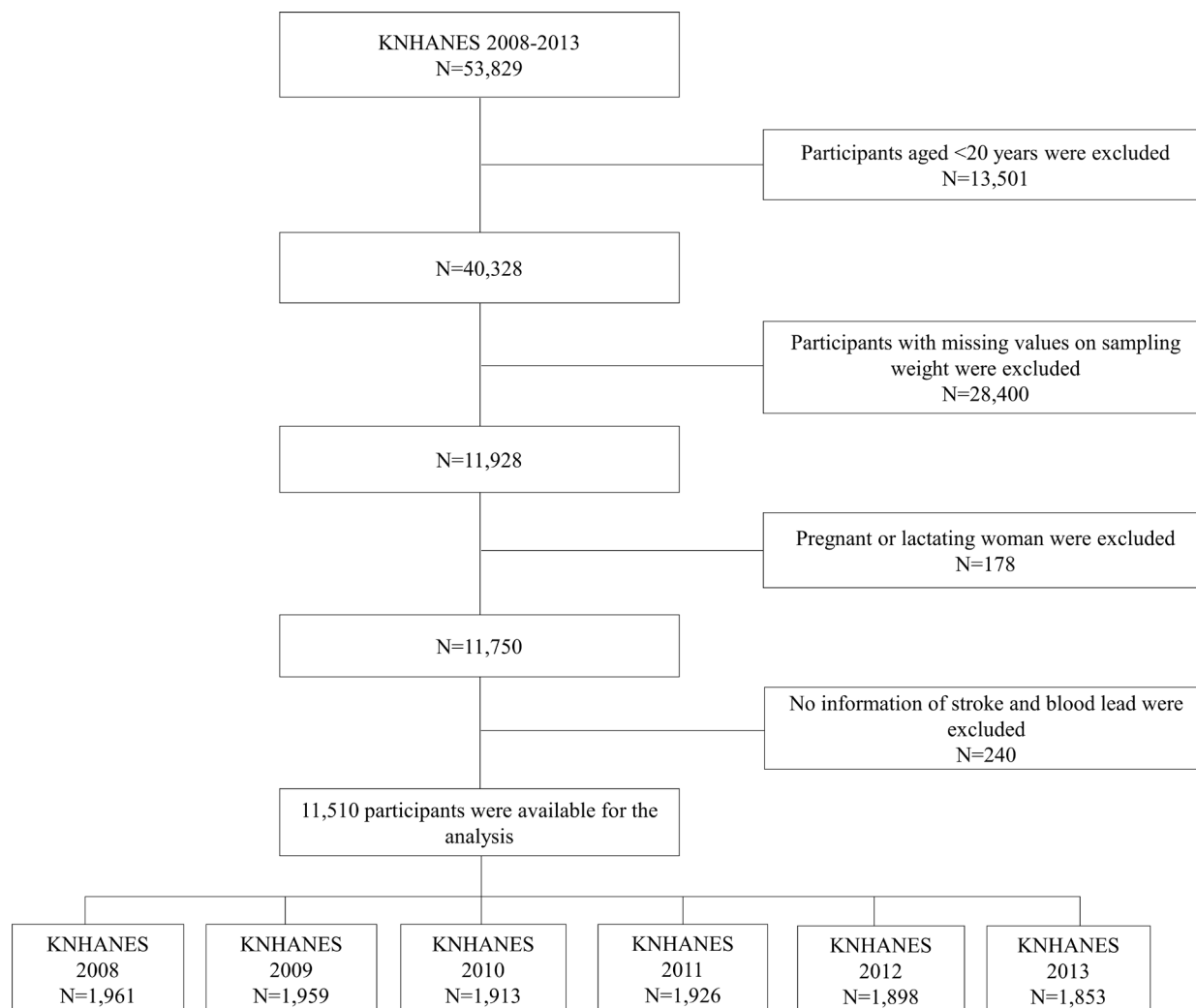


Figure 1 Flow diagram of present study. KNHANES, Korea National Health and Nutrition Examination Survey.

Written informed consent was obtained from all participants and the KNHANES data sets which had available data in our study were approved by the Institutional Review Board (IRB) of the Korea CDC (KCDC) (IRB numbers: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C and 2013-12EXP-03-5C).

General characteristics

The demographic characteristic and lifestyle information included age, sex, education level, household income level, smoking status, alcohol consumption, physical activity and family history of stroke, which were obtained from the health interview and health examination. Education level was categorised as less than high school graduation and high school graduation or more. Household income level was divided into low, mid-low, mid-high and high groups. Smoking status was categorised as former or current smoker and non-smoker. Alcohol consumption was computed by multiplying the quantity of alcohol consumed by the daily frequency of consumption. Physical activity was defined as metabolic equivalents of task (MET-hour/week) and was classified as follows: low, <20 METs-hour/week; middle, 20–<40 METs-hour/week; high, ≥40 METs-hour/week. Family history of stroke was obtained from the health examination and defined as having at least one parent with diagnosed stroke.

Measurement of blood lead concentration

Blood heavy metal concentrations were measured part of the total examined group in KNHANES and was conducted in the Neodin Medical Institute. Blood lead concentration was measured by graphite furnace atomic absorption spectrometry with Zeeman background correction using a PerkinElmer AAnalyst 600 instruments (PerkinElmer, Finland).

Definition of disease

Obesity status was classified as underweight or normal (<23 kg/m²) or overweight or obese (≥23 kg/m²) according to the body mass index criteria for Asian populations from the WHO.³² Hypertension was defined as those with systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, antihypertensive medicine use or physician diagnosis of hypertension. Dyslipidaemia was defined as having at least one of the following criteria:³³ (1) hypercholesterolaemia: total cholesterol ≥240 mg/dL or use of lipid-lowering agents; (2) hypo-high density lipoprotein (HDL) cholesterolaemia: HDL cholesterol <40 mg/dL; (3) hypertriglyceridaemia: triglyceride ≥200 mg/dL; (4) hyper-low density lipoprotein (LDL) cholesterolaemia: LDL cholesterol ≥160 mg/dL or use of lipid-lowering agents or (5) physician diagnosis of dyslipidaemia. Diabetes mellitus was defined as fasting plasma glucose level ≥126 mg/dL,³⁴ diabetes treatments (insulin injection or oral hypoglycaemic agent) or physician diagnosis of diabetes. Stroke, the main outcome, was defined

as physician diagnosis, current presence of stroke or treatment for stroke.

Statistical analysis

Statistical analyses considered the multistage, stratified and clustered probability sampling design using SURVEY procedures in SAS (Statistical Analysis System V.9.4). Based on their median blood lead concentrations, the participants were categorised into the low-level (≤2.189 µg/dL) or high-level (>2.189 µg/dL) group. The general characteristics were compared according to these groups and are presented as frequencies and percentage or means and SDs. The differences between the two groups were assessed by χ^2 tests and general linear regression analysis. Multivariable logistic regression analysis was used to calculate the ORs and 95% CIs for the association between blood lead level and prevalent stroke. The potential confounding factors were determined through preliminary analysis and literature review^{18 19 25 35} and were adjusted as four models: (1) model 1: unadjusted; (2) model 2: adjusted for age, sex and body mass index; (3) model 3: additionally adjusted for education level, household income level, smoking status, alcohol consumption and physical activity; and (4) model 4: additionally adjusted for family history of stroke, dyslipidaemia and diabetes mellitus. The effect modifiers were confirmed using multiplicative terms in the fully adjusted model (model 4). Missing values for confounding factors were excluded from these analyses. All statistical analyses were performed using SAS V. 9.4 and statistical significance set at $\alpha=0.05$.

Patient and public involvement

The KNHANES raw data were provided except personal identification information. The design of this research was done without the study population involvement.

RESULTS

The mean blood lead concentration of overall participants was 2.39±1.18 µg/dL. The general characteristics of the participants according to blood lead level are shown in table 1. The average blood lead concentrations of the low-level and high-level groups were 1.59±0.38 and 3.18±1.18 µg/dL, respectively. Higher blood lead concentrations (>2.189 µg/dL) were observed for men ($p<0.001$), older participants ($p<0.001$), smokers ($p<0.001$), higher alcohol consumption ($p<0.001$), higher physical activity ($p<0.001$), overweight or obese ($p<0.001$) and high rate of family history of stroke ($p<0.001$). Furthermore, the proportions of participants with hypertension ($p<0.001$), dyslipidaemia ($p<0.001$) and diabetes mellitus ($p<0.001$) were higher in the high-level group than in the low-level group. Participants with lower blood lead concentration (≤2.189 µg/dL) had significantly higher household income ($p=0.002$) and education level ($p<0.001$).

Table 2 presents the ORs and 95% CIs of the associations between blood lead level and stroke. In the unadjusted

Table 1 General characteristics according to blood lead, KNHANES 2008–2013 (n=11 510)

	Blood lead levels		P value
	Low ($\leq 2.189 \mu\text{g/dL}$)	High ($> 2.189 \mu\text{g/dL}$)	
Number of participants	5756	5754	
Blood lead ($\mu\text{g/dL}$)	1.59 \pm 0.38	3.18 \pm 1.18	
Age (years)	41.20 \pm 14.95	49.71 \pm 13.62	<0.001
Sex (women)	3756 (65.25)	1976 (34.34)	<0.001
Household income			0.002
Low	1392 (24.43)	1519 (26.74)	
Mid-low	1392 (24.43)	1451 (25.55)	
Mid-high	1437 (25.22)	1358 (23.91)	
High	1476 (25.91)	1352 (23.80)	
Education level			<0.001
Less than high school graduation	1248 (21.71)	2146 (37.37)	
High school graduation or more	4500 (78.29)	3596 (62.63)	
Smoking status			<0.001
Non-smoker	3894 (67.72)	2335 (40.66)	
Former or current smoker	1856 (32.28)	3408 (59.34)	
Alcohol consumption (cup/day)	0.54 \pm 1.17	1.31 \pm 1.96	<0.001
Obesity status			<0.001
Underweight/normal	2871 (49.97)	2183 (38.08)	
Overweight/obese	2875 (50.03)	3550 (61.92)	
Physical activity*			<0.001
Low	2959 (51.49)	2582 (44.99)	
Middle	1154 (20.08)	1068 (18.61)	
High	1634 (28.43)	2089 (36.40)	
Family history of stroke (yes)	345 (9.05)	392 (12.17)	<0.001
History of disease (yes)			
Hypertension	1097 (19.06)	1871 (32.52)	<0.001
Diabetes mellitus	434 (7.67)	551 (9.80)	<0.001
Dyslipidaemia	1630 (28.32)	2210 (38.41)	<0.001

Values are n (%) or mean \pm SD.

*Physical activity was categorised as follows: low, <20 METs-hour/week; middle, 20 – <40 METs-hour/week; high, ≥ 40 METs-hour/week.

KNHANES, Korea National Health and Nutrition Examination Survey; MET, metabolic equivalents of task.

model (model 1), we observed that the high-level group ($>2.189 \mu\text{g/dL}$) had higher odds of stroke than the low-level group ($\leq 2.189 \mu\text{g/dL}$) (OR: 1.84, 95% CI: 1.19–2.85). However, in the fully adjusted model (model 4),

Table 2 The OR of stroke and 95% CI according to blood lead (n=11 510)

	Blood lead levels	
	Low ($\leq 2.189 \mu\text{g/dL}$)	High ($> 2.189 \mu\text{g/dL}$)
	OR	OR (95% CI)
Stroke		
No. of cases	60	114
Model 1	1	1.84 (1.19–2.85)
Model 2	1	1.09 (0.67–1.76)
Model 3	1	1.03 (0.63–1.67)
Model 4	1	1.30 (0.66–2.58)

Model 1: unadjusted.

Model 2: adjustment for age, sex and body mass index.

Model 3: model 2 plus additional adjustments for education level, household income level, smoking status, alcohol consumption and physical activity.

Model 4: model 3 plus additional adjustments for family history of stroke, dyslipidaemia and diabetes mellitus.

the blood lead level was not significantly associated with the stroke (OR: 1.30, 95% CI: 0.66–2.58).

Our study found that hypertension was an effect modifier (p for interaction=0.007) and conducted a stratified analysis according to hypertension status (table 3). This association was significant among participants with hypertension, and the high-level group had 2.36-fold higher odds of stroke ($>2.189 \mu\text{g/dL}$; OR: 2.36, 95% CI: 1.02–5.44) compared with the low-level group ($\leq 2.189 \mu\text{g/dL}$). No association between blood lead and stroke was observed in participants with normal blood pressure (OR: 0.42, 95% CI: 0.13–1.38).

DISCUSSION

The present study examined the association between blood lead level and stroke in Korean adults using data from the KNHANES 2008–2013. The results showed that blood lead levels were not significantly associated with stroke. However, among participants with hypertension, higher blood lead concentrations were associated with the higher risk of prevalent stroke compared with lower blood lead levels.

Lead, as an environmental toxic metal, is ubiquitous in the environment. The sources of lead exposure in the general population are well known gasoline, paint, food, air pollutants and soil pollution.^{14 36 37} Previous studies reported that blood lead concentration was associated with smoking and alcohol drinking.^{38 39} Also, air pollutants considered a source of lead exposure. The particulate matter (PM) among air pollutants contains complex mixture consists of organic carbon, metal including lead and cadmium.^{40 41} Lead within the airborne PM can enter and accumulate the body through the airborne PM. In Canada, the main source of lead exposure is food.⁴² Moreover, water, dust, paint, soil and lead-contaminated

Table 3 The OR of stroke and 95% CI according to blood lead, stratified by hypertension status (n=11 510)

		Blood lead levels		P for interaction
		Low ($\leq 2.189 \mu\text{g/dL}$)	High ($> 2.189 \mu\text{g/dL}$)	
		OR	OR (95% CI)	
Hypertension				0.007
No. of cases	39		85	
Model 1	1		1.45 (0.86–2.47)	
Model 2	1		1.39 (0.77–2.50)	
Model 3	1		1.36 (0.75–2.47)	
Model 4	1		2.36 (1.02–5.44)	
Non-hypertension				
No. of cases	21		29	
Model 1	1		1.31 (0.62–2.74)	
Model 2	1		0.59 (0.27–1.30)	
Model 3	1		0.60 (0.27–1.31)	
Model 4	1		0.42 (0.13–1.38)	

Model 1: unadjusted.

Model 2: adjustment for age, sex and body mass index.

Model 3: model 2 plus additional adjustments for education level, household income level, smoking status, alcohol consumption and physical activity.

Model 4: model 3 plus additional adjustments for family history of stroke, dyslipidaemia and diabetes mellitus.

non-food products were considered a source of lead exposure.⁴² Other countries, such as India, Mexico and Vietnam, reported that medication and unregulated cosmetics products were a source of lead.³⁶ In Iran, individuals working in radiator manufacturing or printing factory were associated with blood lead,⁴³ and opium was presented as a new source of lead exposure.⁴⁴ The average blood lead of the present study participants was $2.39 \pm 1.18 \mu\text{g/dL}$, which is lower than the reference of lead level in CDC ($5 \mu\text{g/dL}$).¹⁷ According to the NHANES, the mean blood lead concentration was $1.82 \mu\text{g/dL}$ (range 0.18 – $33.10 \mu\text{g/dL}$),⁴⁵ and the Canada Health Measures Survey reported that blood lead concentration was $1.2 \mu\text{g/dL}$ in aged 20–79 years.⁴⁶ The average blood lead levels for these countries were lower than in our study. Whereas, the studies were presented that the mean blood lead concentrations for German and Iran populations were $3.07 \mu\text{g/dL}$ ⁴⁷ and $5.11 \pm 7.41 \mu\text{g/dL}$,⁴⁸ respectively, and the median level for China was $4.40 \mu\text{g/dL}$,¹⁹ which is relatively higher than our result.

Lead is absorbed from the respiratory or gastrointestinal tracts.⁴⁹ Lead absorbed into the body accumulates primarily in bone, as well as blood or soft tissues such as the brain, kidney and liver.^{13 50 51} Hence, it is known that the exposure of lead induces the toxicity in the kidney and liver.^{52–54} In the brain, lead results in neuronal cell death

leading to memory loss and the pathogenesis of Alzheimer's disease (AD).^{55 56} In this regard, a case–control study showed that the blood lead level is increased in AD compared with that of healthy control (OR: 1.05, 95% CI 1.01–1.09).⁵⁶ Furthermore, in patients with multiple sclerosis, the blood lead level is elevated than that of healthy control (OR: 1.17, 95% CI: 1.001–1.28, per $1 \mu\text{g/L}$ increment).⁵⁷ Growing evidence showed that lead exposure affects cardiovascular health.^{58 59} Lead exposure is associated with negative effects on cardiovascular health. The possible mechanisms to explain this association include increased oxidative stress in response to lead,^{60 61} elevated reactive oxygen species may oxidise nitric oxide, leading to lipid damage.⁶⁰ In addition, lead induces inflammation via activation of nuclear transcription factor- κB , which results in impairment of cerebral blood vessels.⁶¹ Finally, high blood pressure and subsequent arteriosclerosis are caused by vasomotor tone.^{12 62} These mechanisms can lead to cardiovascular disease including stroke.

Until now, epidemiological studies have observed inconsistent results on the association between blood lead level and stroke. Accumulating evidence showed that the level of lead in blood is associated with cardiovascular disease, including stroke.^{18 19 59} In a prospective cohort study on the association between blood lead concentration below $10 \mu\text{g/dL}$ and mortality due to stroke in the US adults, the highest tertile of blood lead had a 2.51-fold increased risk of incident mortality than that for the lowest tertile (HR: 2.51, 95% CI: 1.20–5.26).¹⁸ The SPECT-China showed a significant association between blood lead level and the prevalence of cardiovascular disease in women (OR: 1.93, 95% CI: 1.22–3.04, p for trend < 0.01).¹⁹ A meta-analysis that pooled estimates on the association between blood lead level and the incidence of stroke reported that blood lead increased the risk of stroke (RR: 1.63, 95% CI: 1.14–2.34).⁵⁹ Recently, a case–control study also reported that the lead in the blood is significantly associated with acute stroke (OR: 1.04, 95% CI: 1.02–1.07 per $1 \mu\text{g/dL}$ in blood lead), suggesting a risk factor for ischaemic stroke.⁶³ Nevertheless, other studies did not observe a significant association. A prospective cohort study of the effect of blood lead on mortality due to stroke reported that the risk of stroke mortality did not differ according to blood lead level in older women (OR: 1.13, 95% CI: 0.34–3.81).⁶⁴ A case–control study showed a non-significant association between serum lead and acute ischaemic stroke (OR: 0.97, 95% CI: 0.91–1.02).⁶⁵ In present study, we found that blood lead was not associated with stroke.

Meanwhile, our findings indicate that hypertension status influenced the association between lead and stroke. No association was identified between blood lead level and stroke in participants with normal blood pressure; however, lead level was positively associated with prevalence of stroke in individuals with hypertension. The previous study was shown that there was a significant interaction between chronic obstructive pulmonary disease and blood lead on stroke.⁶⁶ Other studies have reported hypertension to be an effect modifier of



the association between blood lead and chronic kidney disease related to a significantly higher risk of chronic kidney disease in patients with hypertension.^{54–67} High blood pressure progressively damages blood vessels,⁶⁸ these weakened blood vessels may be blocked and ruptured by plaques and thrombus.⁶⁹ Thus, patients with hypertension have a higher risk of stroke compared with that in patients with normotension.^{69–70} Lead as a heavy metal contributes to elevated blood pressure.^{62–71} Patients with hypertension were often had high lead concentrations^{28–72–74} and resistant hypertension was also related to high lead levels.⁷⁵ Moreover, lead exposure in individuals with hypertension might contribute to the risk of stroke due to the hypertensive effects of lead, including high blood pressure and impaired blood vessels. Additional studies are required to determine the mechanism of this association.

The reference blood lead level for adults was previously set to 10 µg/dL, but has been readjusted to 5 µg/dL since 2015. However, we observed that those with hypertension in the group with blood lead concentration above 2.189 µg/dL, below readjusted reference of blood lead, were associated with higher prevalence of stroke. In addition, the several studies reported that blood lead concentration as low as 2 µg/dL was negative effect of various diseases including hypertension and cardiovascular disease.^{18–67–76–77} Our result was similar to these previous studies. Further, researches on health impact of lower lead concentration than reference blood lead are required.

Our study has several limitations. First, the causality between blood lead level and stroke was not clearly determined (reverse causal relationship) due to the cross-sectional analysis. Second, while bone lead concentrations are more reflective of long-term exposure (half-life 10 years) rather than blood lead concentration (half-life 1–2 months),^{50–73} these data were not available in the KNHANES. Third, lead exposure by occupational and highly contaminated areas was not considered because the KNHANES data do not provide detailed information to divided lead workers and high lead exposure areas. Despite these limitations, this study sample, the KNHANES, is representative of the Korean population; thus, our results are generalisable to Korean adults. Furthermore, this study provides evidence of this association in Korean adults.

CONCLUSION

Our findings indicated that blood lead concentration was not associated with stroke. However, in participants with hypertension, blood lead level was associated with higher risk of prevalent stroke. These results suggest the potentially harmful effects of blood lead on stroke in individuals with hypertension. Large-scale prospective cohort studies are required to identify the causality between blood lead and risk of stroke.

Contributors MK conducted the analysis and wrote the draft of the manuscript. S-MY, JJ and CJ contributed to data interpretation and review of the manuscript. YHK designed and supervised the manuscript. All authors read and approved the final version.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the IRB of the KCDC with approval numbers (2017-05-06-C-A).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data used in this study are available in the Korea Centers for Disease Control and Prevention (KCDC) and KNHANES repository (https://knhanes.cdc.go.kr/knhanes/sub03/sub03_02_02.do).

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ORCID iD

Young Ho Koh <http://orcid.org/0000-0001-9934-5321>

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