Association between heavy metals, high-sensitivity C-reaction protein and 10-year risk of cardiovascular diseases among adult Korean population

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The prevalence of cardiovascular diseases (CVDs) in Korea tends to be increasing. It has worsened during the COVID-19 pandemic. Increasing evidence shows heavy metals are associated with increased CVD risk. We aimed to determine the association between the serum heavy metal levels and 10-year risk of CVDs and to predict risks of CVDs based on marginal effects. Heavy metals were measured by a graphite furnace atomic absorption spectrometry and direct mercury analyzer. The results show a significant relationship between the increase in cadmium, lead, mercury, hs-CRPs levels and the 10-year risk of CVD after adjustment for serum cotinine, age group, sex, body mass index, a family history of CVDs, diabetes or hyperlipidemia, high-risk drinking, physical activity, and diabetes. A doubling of serum cadmium, lead, mercury, and hs-CRP was associated with the increase in the 10-year risk of CVD by 0.14%, 0.10%, 0.11% and 0.22%, respectively. Therefore, a special concern should be given to the harmful impacts of heavy metals on the 10-year risk of CVD. It is important to develop a prevention strategy targeting the high-risk population to slow down this progression to risk factors related to heavy metals and reduce prevalence. Remarkably, hs-CRP is the most validated and widely used inflammatory marker, and could be a potential clinical value in predicting and monitoring CVDs.

Cardiovascular diseases (CVDs), including heart disease (i.e., myocardial infarction, angina, and heart failure) and cerebrovascular disease, are a leading cause of death worldwide. In South Korea, CVDs are one in every five deaths.

Over the past few decades, rapid changes in lifestyles and diets such as (smoking, alcohol consumption, consumption of high-unsaturated fat diets, or low energy diets) have led to a rapid increase in the prevalence of non-communicable diseases (NCDs), especially CVDs in South Korea. Furthermore, inherited DNA sequence variants are known to contribute to the conferring of risk for CVDs; however, the effects of heavy metals on the risk factors of CVDs are also important.

Rapid industrialization, urbanization and economic growth have increased heavy metal exposure. Lead exposure is due to gasoline, cigarette smoke, manufacturing processes, and domestic lead-based paints. Cadmium exposure can be attributed to cigarette smoke and contaminated food or water, whereas contaminated seafood (e.g., fish, shellfish) is primary source of mercury. Accumulated mercury in organs is associated with the development of carotid atherosclerosis, whereas lead and cadmium may disturb blood clotting and increase the risk of CVDs. Furthermore, heavy metals catalyzes the production of reactive oxygen species (ROS) and induces inflammatory mediators leading to damage to endothelial vascular cells.

Prevention and management have become a top priority due to the increased global burden of CVDs, especially in the situation of the Coronavirus disease-19 (COVID-19) pandemic. Therefore, the cardiovascular risk assessment should be carried out to classify people who most likely benefit from primary prevention. The Framingham Risk Score recommended by the National Cholesterol Education Program (Adult Treatment Panel III) is the most common assessment tool to evaluate a 10-year risk of CVD. However, few studies have explored the correlations between serum heavy metal levels and risk of CVDs among the adult population with or without...
diabetes on national scales. In this study, we present evidence that increased serum heavy metal levels are related to increased development of the 10-year risk of CVD among the Korean population. We also show the inflammatory marker, which could be a potential clinical value in predicting and monitoring CVDs.

**Results**

9602 participants (mean age 47.3 ± 15.2, min–max: 20–79) that participated in the KNANES 2009–2013, 2016–2017 surveys were included. Table 1 shows baseline characteristics according to gender. Males were significantly more likely to be smokers, unmarried, have high-risk drinking.

The average 10-year risk of CVD was 7.36 ± 7.34. The majority of the subjects were identified in the low-risk (67.3%) category; 21.9% at medium risk, and only 11 percent at high risk. Geometric mean serum cadmium, lead, mercury, and high-sensitivity C-reactive protein (hs-CRP) levels were 0.97 µg/L (95%CI: 0.95–0.97), 2.02 µg/dL (1.10) (95%CI: 2.00–2.03), 3.71 µg/L (3.52) (95%CI: 3.66–3.75), and 0.72 mg/L (95%CI: 0.70–0.75), respectively.

Table 2 shows the Pearson correlation coefficients (r) between the 10-year risk of CVD, cardio-metabolic risk factors, and dietary intake by gender. We found that strong significant correlations were pointed out between the 10-year risk of CVD and age (r = 0.818 for males and r = 0.828 for females); significant positive correlations were noted between 10-year risk of CVD, total cholesterol (r = 0.515), LDL-C (r = 0.540) and systolic blood pressure (r = 0.645) in females.

Figure 1 shows the levels of the 10-year risk of CVD according to the quartiles of serum cadmium, lead, mercury, and hs-CRP among the Korean population. The level of the 10-year risk of CVD was significantly higher among subjects with high serum heavy metal levels or serum hs-CRP levels than those with low serum heavy metal levels or serum hs-CRP levels.

Figure 2 shows the prediction of 10-year risk of CVD among subjects with or without diabetes by heavy metals and hs-CRP. A doubling of serum cadmium, lead and mercury was associated with the increase in the 10-year risk of CVD by 5.47% (β = 5.47, 95% CI: 4.93–6.00, p < 0.001), 5.53% (β = 5.53, 95% CI: 5.02–6.04, p < 0.001), and 5.86% (β = 5.86, 95% CI: 5.33–6.40, p < 0.001) among subjects with diabetes, respectively. Similarly, among subjects with diabetes, the 10-year risk of CVD increased by 4.92% (β = 4.92, 95% CI: 4.16–5.68, p < 0.001) with a twofold increase in serum hs-CRP levels.

An increase in serum cadmium, lead, mercury and hs-CRP was associated with an increase in cardiometabolic risk factors in both males and females. As presented in Table 3, age, BMI, waist circumference, total cholesterol, LDL-C, triglyceride, HDL-C, HbA1c, fasting glucose, energy intake, hemoglobin, hematocrit, BUN, creatinine, ALT, AST, systolic blood pressure, and diastolic blood pressure increased significantly among quartiles of serum cadmium, lead, mercury and hs-CRP.

Table 4 demonstrates the results of multiple regression analysis of the 10-year risk of CVD. The results show a significant relationship between the increase in cadmium, lead, mercury and CRP levels and 10-year risk of CVD after adjustment for age group, serum cotinine, sex, body mass index, a family history of CVDs or diabetes, or hyperlipidemia, high-risk drinking, physical activity, and diabetes. A doubling of serum cadmium, lead, mercury, and hs-CRP was associated with the increase in the 10-year risk of CVD by 0.14% (β = 0.14, 95% CI: 0.05–0.23, p = 0.003), 0.10% (β = 0.10, 95% CI: 0.02–0.21, p < 0.001), 0.11% (β = 0.11, 95% CI: 0.04–0.18, p = 0.003) and 0.22% (β = 0.22, 95% CI: 0.16–0.29, p < 0.001), respectively.

Figure 3 shows the marginal effect of the levels of serum heavy metals, and hs-CRP on the 10-year risk of CVD by age group after adjustment for potential confounders among the Korean population. The effect of heavy metals and hs-CRP showed a similar trend. An increase in serum cadmium, lead, mercury and hs-CRP was associated with an increase in the 10-year risk of CVD in each age group.

**Discussion**

Our findings include empirical data that continues to draw on an important volume of previous studies to support the association between heavy metals and the 10-year risk of CVD among adult Koreans at the national level. More specifically, an increase in serum levels of cadmium, lead, mercury or CRP was associated with an increase in the 10-year risk of CVD.

The strong positive association found in our study between lead and 10-year risk of CVD emphasizes lead exposure as an important public health problem and concern. The mediation of accelerated systolic blood pressure and renal damage is two main mechanisms through which lead has been involved in the risk of CVDs. Besides, another hypothesis showed that the association of lead with atherosclerosis due to lead-induced oxidative stress and inflammation. On the other hand, several studies have also reported on the association between exposure to cadmium or lead and elevated blood pressure. It could be explained that lead exposure may alter the renin–angiotensin system and cause disorders of sodium balance, raise vasoconstrictor prostaglandins, lower vasoactive agonists.

We found that there was a positive association between levels of cadmium and the 10-year risk of CVD. The adverse effects of cadmium on the vascular system are attributed to being mediated by inflammation, oxidative stress, and endothelial cell damage, which could lead to atherosclerosis. Furthermore, Cadmium may cause CVDs through its adverse effects on the kidney due to nephrotoxicity and direct vasoconstriction. Serum cadmium levels are also a positive correlation with hypertension. On the other hand, oxidative stress induced by exposure to cadmium or lead, causes DNA damage and oxidizes protein thiol groups. Cadmium or lead may also destroy blood clotting and provoke the production of inflammatory cytokines and anti-thrombotic agents.

The exact biological mechanisms by which mercury produces toxic effects on CVDs remain unclear. However, our findings show higher serum mercury levels are associated with a significantly higher risk of CVD.
## Demographic and social characteristics

|                          | Males n = 4724 | Females n = 4878 |
|---------------------------|----------------|------------------|
| **Age (year)**            | 47.76 ± 15.25  | 46.87 ± 15.16    |
| **Age group (%)**         |                |                  |
| 20–34                     | 1162 (24.6)    | 1121 (23.0)      |
| 35–39                     | 528 (11.2)     | 522 (10.7)       |
| 40–44                     | 513 (10.9)     | 448 (9.2)        |
| 45–49                     | 462 (9.8)      | 511 (10.5)       |
| 50–54                     | 467 (9.9)      | 511 (10.5)       |
| 55–59                     | 489 (10.4)     | 543 (11.1)       |
| 60–64                     | 398 (8.4)      | 414 (8.5)        |
| 65–69                     | 349 (7.3)      | 409 (8.4)        |
| 70–74                     | 218 (4.6)      | 235 (4.7)        |
| 75–79                     | 138 (2.9)      | 164 (3.4)        |
| **Marital status (%)**    |                |                  |
| Married                   | 3694 (78.2)    | 4148 (85.0)      |
| Living alone              | 1030 (21.8)    | 730 (15.0)       |
| **Residential areas (%)** |                |                  |
| Urban                     | 3812 (80.7)    | 3961 (81.2)      |
| Rural                     | 912 (19.3)     | 917 (18.8)       |
| **Occupation (%)**        |                |                  |
| Managers, professional    | 756 (16.0)     | 578 (11.9)       |
| Office worker, clerical workers | 602 (12.7) | 398 (8.2) |
| Service workers, sales workers | 549 (11.6) | 710 (14.6) |
| Agriculture, forestry and fishing workers | 325 (6.9) | 221 (4.5) |
| Craft, plant and machine operators and assemblers | 995 (21.1) | 136 (2.8) |
| Elementary occupations    | 363 (7.7)      | 446 (9.0)        |
| Unemployed                | 1134 (24.0)    | 2300 (49.0)      |
| **Education level (%)**   |                |                  |
| ≤ Middle school           | 1076 (23.2)    | 1706 (35.6)      |
| High school               | 1743 (37.6)    | 1590 (33.2)      |
| ≥ College                 | 1816 (39.2)    | 1495 (31.2)      |
| **Monthly household income (%)** |        |                  |
| < 2000                    | 1232 (26.1)    | 1457 (29.9)      |
| ≥ 2000 and < 4000         | 1581 (33.5)    | 1530 (31.3)      |
| ≥ 4000 and < 6000         | 1027 (21.7)    | 975 (20.0)       |
| ≥ 6000                    | 884 (18.7)     | 916 (18.8)       |
| **BMI group (%)**         |                |                  |
| < 18.5                    | 112 (2.4)      | 242 (5.0)        |
| ≥ 18.5 and < 25           | 2786 (59.3)    | 3169 (65.0)      |
| ≥ 25 and < 30             | 1622 (34.3)    | 1232 (25.2)      |
| ≥ 30                      | 190 (4.0)      | 235 (4.8)        |
| **Smoking status (%)**    |                |                  |
| Non/ex-smoker             | 2412 (50.8)    | 4562 (94.1)      |
| Current smoker            | 2540 (49.2)    | 288 (5.9)        |
| Cotinine verified smokers (%) |        |                  |
| No                        | 2549 (54.0)    | 4380 (89.8)      |
| Yes                       | 2175 (46.0)    | 498 (10.2)       |
| **High-risk drinking status (%)** |        |                  |
| No                        | 3905 (80.1)    | 4724 (100.0)     |
| Yes                       | 973 (19.9)     | 0 (0.0)          |
| **Physical activity (%)** |                |                  |
| Not regular               | 3341 (70.7)    | 3426 (70.2)      |
| Regular                   | 1383 (29.3)    | 1452 (29.8)      |
| **Family history of CVDs (%)** |        |                  |
| No                        | 3223 (68.2)    | 3691 (63.4)      |
| Yes                       | 1501 (31.8)    | 1787 (36.6)      |
| **Continued**             |                |                  |
development, which is consistent with previous studies. It could be explained that mercury exposure may increase the formation of ROS, free radicals, ROS, and superoxide anions, and reduce antioxidant enzyme activity (e.g., glutathione peroxidase, catalase, and superoxide dismutase), which can cause an increased risk of developing CVDs. Taken together, these mechanisms support our results about the association between serum cadmium, lead, mercury levels and 10-year risk of CVD.

Our findings show that the association of aging with an increase in serum cadmium and lead; serum cotinine levels were positively correlated with serum cadmium and lead, which was in line with the previous studies. It partly explained why strong significant correlations were pointed out between the 10-year risk of CVD and

| Variables                     | Male n = 4724 | Female n = 4878 |
|-------------------------------|--------------|----------------|
| Age (year)                    | 0.818        | 0.828          |
| BMI (Kg/m²)                   | 0.137        | 0.374          |
| Waist circumference (cm)      | 0.271        | 0.456          |
| Total cholesterol (mg/dL)     | 0.357        | 0.515          |
| LDL-C (mg/dL)                 | 0.306        | 0.540          |
| Triglyceride (mg/dL)          | 0.248        | 0.376          |
| HDL-C (mg/dL)                 | −0.207       | −0.255         |
| HbA1c (%)                     | 0.301        | 0.364          |
| Fasting glucose (mg/dL)       | 0.288        | 0.296          |
| Energy intake (Kcal)          | −0.127       | −0.101         |
| Hemoglobin (g/dL)             | −0.146       | 0.114          |
| ALT (U/L)                     | 0.066        | 0.224          |
| AST (U/L)                     | 0.085        | 0.264          |
| SBP (mmHg)                    | 0.355        | 0.645          |
| DBP (mmHg)                    | 0.151        | 0.421          |
| Serum creatinine (µmol/L)     | 0.040        | 0.101          |
| BUN (mmol/L)                  | 0.223        | 0.335          |
| Serum cotinine (ng/mL)        | 0.116        | 0.129          |
| Vitamin B1 (mg)               | −0.093       | −0.010         |
| Vitamin B2 (mg)               | −0.118       | −0.134         |
| Vitamin B3 (mg)               | −0.125       | −0.146         |
| Vitamin C (mg)                | −0.046       | −0.054         |
| Total vitamin A (µg)          | 0.030        | −0.009         |
| Omega 3 (g)                   | −0.019       | −0.067         |
| Omega 6 (g)                   | −0.232       | −0.225         |
| Serum Cd (µg/L)               | 0.288        | 0.376          |
| Serum Pb (µg/dL)              | 0.245        | 0.243          |
| Serum Hg (µg/L)               | 0.221        | 0.217          |
| hs-CRP (mg/L)                 | 0.194        | 0.226          |

Table 1. Demographic distribution of participants in Korea from 2009 to 2017. BMI body mass index (kg/m²), CVDs Cardiovascular diseases. *Thousand won.

Table 2. Pearson bivariate correlation between the 10-year risk of CVD and cardiometabolic risk factors, dietary intake by sex. BUN blood urea nitrogen, HDL-C high-density lipoprotein cholesterol, ALT alanine aspartate aminotransferase, AST aspartate aminotransferase, LDL-C low-density lipoprotein cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure.
age. Of note, an increase in serum cadmium and lead levels was associated with an increase in serum cotinine levels, which was in agreement with the previous study\textsuperscript{32}.

Interestingly, we also found that the effect of heavy metals (cadmium, lead and mercury) on lipid metabolism, especially total cholesterol and LDL-C, which concurs with the previous studies. For example, Kristal-Boneh et al. showed that the subjects exposed to lead had higher serum total cholesterol levels compared to those that did not\textsuperscript{33}. Cho et al. also found a strong link between mercury exposure, LDL-C levels, and total cholesterol in the Korean general population\textsuperscript{34}. In vivo studies also showed that an increase in serum cadmium levels was associated with increased levels of serum total cholesterol, LDL-C and triglyceride, and reduced HDL-C and glutathione levels\textsuperscript{35,36}. Several mechanisms have been proposed to explain their associations with total cholesterol. First, lead may enhance hepatic gene expression of lanosterol 14α-demethylase (CYP51), which is a cytochrome P450 isoform, causing an increase in cellular cholesterol and total cholesterol levels\textsuperscript{37}. Furthermore, the suppression of catabolic enzymes (e.g., 7 alpha-hydroxylase) and the activation of cholesterol synthesis enzymes (e.g., farnesyl diphosphate synthase, 3-hydroxyl-3-methylglutaryl-CoA reductase, squalene synthase) were associated with lead-mediated hypercholesterolemia\textsuperscript{37}. Second, mercury may increase lipid peroxidation, serum oxidized LDL, and oxidation of LDL. These processes make metabolism of LDL difficult and result in its subsequent accumulation\textsuperscript{38}. Third, Cadmium may deplete protein-bound sulphhydril groups and glutathione, which leads to an increase in the production of ROS such as hydroxyl radicals, superoxide ion, and hydrogen peroxide. These ROS are known to induce increased excretion of urinary lipid metabolites and lipid peroxidation\textsuperscript{39}.

hs-CRP is an independent risk factor for CVDs\textsuperscript{40}. Another study found that hs-CRP levels above 10 mg/L are associated with a greater than 4% risk of developing a fatal CVD in 10 years\textsuperscript{41}. Another study also reported the hs-CRP level above 10 mg/L is related to an over 4 percent risk of developing a fatal CVD in 10 years\textsuperscript{42}. In several aspects of atherogenesis, hs-CRP plays a fundamental role, including the macrophage lipid uptake, release of proinflammatory cytokines, activation of the complement pathway, promotes endothelial dysfunction, induces tissue factor expression in monocytes and inhibits the development of nitric oxide\textsuperscript{43}. These findings support our results that an increase in serum levels of hs-CRP was associated with an increase in the 10-year risk of CVDs.

Heavy metals such as cadmium, lead or mercury are toxic to the human body and can trigger different diseases, especially CVDs\textsuperscript{44}. As a result, the prevalence of CVDs and exposure to heavy metal in Korea tends to be increasing\textsuperscript{45-47}. These have worsened during the COVID-19 pandemic\textsuperscript{48}. Unfortunately, the dramatic global increase in urbanization and industrialization has increased the risk of exposure to heavy metals\textsuperscript{32}. For example, cadmium is abundant in groundwater and common foods such as rice, vegetables\textsuperscript{24}. Remarkably, serum cadmium, lead and mercury levels are appropriate biomarkers for recent exposures to lead and cadmium\textsuperscript{49,50}. Therefore, special concern should be given to the harmful impacts of heavy metals on the 10-year risk of CVDs. It is important to develop a prevention strategy targeting the high-risk population to slow down this progression.
to risk factors related to heavy metals and reduce prevalence. hs-CRP is the most validated and widely used inflammatory marker, and could be a potential clinical value in predicting and monitoring CVDs.

This large-scale Korean study is to report the effect of heavy metals on the 10-year risk of CVD at a national level. However, it has several limitations. First, the cross-sectional method used prevented evaluation of causality between 10-year risk of CVD and serum heavy metals. Second, actual CVD events (e.g., stroke, coronary heart disease or heart failure) were not evaluated. Third, the levels of heavy metals in the whole blood were not measured.

Methods
Study population. The heavy metal dataset of the Korean National Health and Nutrition Examination Survey (KNHANES) IV (2009), KNHANES V (2010–2012), KNHANES VI (2013), and KNHANES VII (2016–2017)\(^1\), a representative annual survey of the blood heavy metal concentrations, health, and nutritional status in the civilian, non-institutionalized Korean general population, was used. A total of 10,533 (2009), 8958 (2010), 8518 (2011), 8058 (2011), 8150 (2013), and 8127 (2017) subjects participated in the KNHANES. Of the 60,362 participants who underwent the survey from 2009–2013 to 2016–2017, we excluded 14,369 subjects less than 20 years old, 159 subjects more than 80 years old, 31,286 records missing serum Pb, Cd, missing laboratory test results [total cholesterol (1), HDL (3), systolic blood pressure (34), cotinine (4879)], and information on hypertension treatment (30). Consequently, a total of 9602 were eligible for data analysis. All participants in KNHANES provided written informed consent before examinations, which were performed by the Health and Nutrition Examination Department of the Korea Centers for Disease Control and Prevention. This study was approved by the KNHANES inquiry commission (IRB Approval numbers: 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C, 2013-12EXP-03-5C). From 2016 to 2017, KNHANES was exempt from review regarding research ethics under the Bioethics and Safety Act.

Determination of serum Pb, and Cd levels. Pb, Hg, and Cd levels in serum were measured as previously described\(^2\). Serum cadmium, lead and mercury concentrations were determined by the NEODIN Medical Institute, certified by the Ministry of Health and Welfare of Korea. These tests meet the requirements of the German External Quality Assessment Scheme, the U.S. CDC, and the Korea Occupational Safety and Health Administration program. cadmium and lead were measured by graphite furnace atomic absorption spectrometry (model AAnalyst 600; Perkin Elmer, Turku, Finland) using Zeeman background correction. Total mercury was measured using a direct mercury analyzer (model DMA-80 Analyzer; Bergamo, Italy). Limits of detection

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Figure 2. The prediction of 10-year risk of CVD among subjects with or without diabetes by heavy metals and hs-CRP.
### (A) Cardiometabolic factors according to the quartiles of serum cadmium levels by gender

| Variables                  | Cadmium quartiles | P-value | Cadmium quartiles | P-value |
|----------------------------|-------------------|---------|-------------------|---------|
| **Age (year)**             | 32.06 ± 11.58     | < 0.001 | 41.28 ± 14.44     | < 0.001 |
| BMI (Kg/m²)                | 24.21 ± 3.59      | 0.046   | 24.37 ± 3.13      | 24.03 ± 3.06 |
| Waist circumference (cm)   | 83.48 ± 9.65      | < 0.001 | 84.58 ± 8.89      | 85.73 ± 8.77 |
| Total cholesterol (mg/dL)  | 179.62 ± 34.55    | < 0.001 | 166.97 ± 36.41    | 190.90 ± 36.73 |
| LDL-C (mg/dL)              | 107.32 ± 28.22    | 0.042   | 114.27 ± 31.32    | 119.14 ± 31.59 |
| Triglyceride (mg/dL)       | 99.45 ± (14.60)   | < 0.001 | 115.00 ± (17.46)  | 147.50 ± 21.63 |
| HDL-C (mg/dL)              | 47.41 ± 10.33     | 0.038   | 47.26 ± 10.70     | 46.18 ± 11.58 |
| HbA1c (%)                  | 5.43 ± 0.66       | < 0.001 | 5.72 ± 1.03       | 5.90 ± 1.04 |
| Fasting glucose (mg/dL)    | 92.89 ± 17.39     | < 0.001 | 99.28 ± 26.57     | 102.68 ± 26.10 |
| Energy intake (Kcal)       | 2446.97 ± 1116.32 | 0.180   | 2428.25 ± 987.62  | 2347.15 ± 961.58 |
| Hemoglobin (g/dL)          | 15.34 ± 1.00      | 0.027   | 15.23 ± 1.08      | 15.29 ± 1.16 |
| Hematocrit (%)             | 45.74 ± 2.98      | 0.117   | 45.43 ± 3.09      | 45.54 ± 3.33 |
| BUN (mmol/L)               | 14.04 ± 3.46      | 0.001   | 14.63 ± 4.22      | 15.43 ± 4.65 |
| Serum creatinine (µmol/L)  | 0.99 ± 0.43       | 0.017   | 0.98 ± 0.23       | 0.96 ± 0.17 |
| ALT (U/L)                  | 18 (10–27)        | < 0.001 | 21 (11–29)        | 22 (11–32) |
| AST (U/L)                  | 20 (13–23)        | < 0.001 | 21 (14–25)        | 22 (15–27) |
| SRF (mmHg)                 | 116.09 ± 12.13    | < 0.001 | 119.05 ± 14.06    | 122.06 ± 15.09 |
| DBP (mmHg)                 | 77.07 ± 8.77      | < 0.001 | 79.00 ± 10.01     | 80.42 ± 11.61 |
| Serum cotinine (µg/L)      | 2.27 (0.19–10.51) | < 0.001 | 3.76 (0.18–69.97) | 29.73 (0.24–1200.65) |

### (B) Cardiometabolic factors according to the quartiles of mercury levels by gender

| Variables                  | Mercury quartiles | p-value | Mercury quartiles | p-value |
|----------------------------|-------------------|---------|-------------------|---------|
| **Age (year)**             | 54.40 ± 19.90     | 0.0003  | 45.02 ± 19.86     | 45.64 ± 17.73 |
| BMI (Kg/m²)                | 22.79 ± 3.62      | 0.001   | 23.50 ± 3.61      | 23.51 ± 3.25 |
| Waist circumference (cm)   | 81.85 ± 9.98      | < 0.001 | 83.41 ± 10.30     | 83.23 ± 9.23 |
| Total cholesterol (mg/dL)  | 181.80 ± 30.00    | < 0.001 | 178.71 ± 34.19    | 185.19 ± 35.84 |
| LDL-C (mg/dL)              | 120.28 ± 35.37    | 0.0002  | 106.10 ± 27.70    | 108.94 ± 31.18 |
| Triglyceride (mg/dL)       | 44.93 ± 11.47     | 0.790   | 46.37 ± 11.45     | 46.62 ± 11.41 |
| HbA1c (%)                  | 5.85 ± 0.92       | 0.285   | 5.73 ± 0.11       | 5.80 ± 1.07 |
| Fasting glucose (mg/dL)    | 98.10 ± 19.92     | 0.220   | 101.88 ± 27.26    | 107.61 ± 27.77 |
| Energy intake (Kcal)       | 1784.09 ± 680.97  | 0.001   | 2213.09 ± 866.77  | 2287.59 ± 945.03 |
| Hemoglobin (g/dL)          | 14.51 ± 1.61      | < 0.001 | 14.94 ± 1.41      | 15.04 ± 1.28 |
| Hematocrit (%)             | 49.33 ± 4.37      | < 0.001 | 47.40 ± 3.78      | 44.99 ± 3.68 |
| BUN (mmol/L)               | 14.36 ± 4.25      | 0.0066  | 13.71 ± 4.55      | 14.54 ± 3.50 |
| Serum creatinine (µmol/L)  | 0.80 ± 0.18       | 0.028   | 0.99 ± 0.24       | 0.96 ± 0.17 |
| ALT (U/L)                  | 16.51 (10–23)     | < 0.001 | 18 (9–26)         | 19 (10–27) |
| AST (U/L)                  | 20 (13–25)        | < 0.001 | 20 (13–25)        | 22 (15–27) |
| SRF (mmHg)                 | 123.45 ± 16.77    | 0.0001  | 120.46 ± 15.96    | 119.42 ± 15.47 |
| DBP (mmHg)                 | 74.26 ± 11.68     | 0.0001  | 77.58 ± 10.15     | 80.66 ± 10.18 |
| Serum cotinine (µg/mL)     | 5.61 (0.21–967)   | 0.350   | 6.81 (0.21–1108.25)| 12.58 (0.24–1180.58)|
Cardiometabolic factors according to the quartiles of serum cadmium, lead, mercury, and hs-CRP levels by gender. BUN blood urea nitrogen, LDL-C low-density lipoprotein cholesterol, ALT alanine aspartate aminotransferase, AST aspartate aminotransferase, DBP diastolic blood pressure. *Median (IQR) and p-value using Kruskal Wallis test.
### Parameters

| Parameters | Cadmium (μg/L) |  |  |  | hs-CRP (mg/L) |  |  |  |
|------------|----------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|            | β | SE   | 95% CI | p-value | β | SE | 95% CI | p-value |
|            | Adjusted R² | 0.773, p < 0.001 |  |  | Adjusted R² | 0.764, p < 0.001 |  |  |

**(A) For cadmium and hs-CRP**

| Serum Cadmium or hs-CRP | 0.135 | 0.046 | 0.045 | 0.225 | 0.003 | 0.222 | 0.033 | 0.157 | 0.287 | < 0.001 |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|---------|
| Serum cotinine (ng/mL)  | 0.0002 | 0.0005 | 0.00006 | 0.0003 | 0.001 | 0.0003 | 0.0007 | 0.0001 | 0.0004 | < 0.001 |

**Age group (%)**

| 20–34 | Refer | Refer | Refer |
| 35–39 | 5.334 | 0.114 | 5.110 | 5.559 | < 0.001 | 5.077 | 0.154 | 4.776 | 5.378 | < 0.001 |
| 40–44 | 5.453 | 0.119 | 5.220 | 5.687 | < 0.001 | 5.259 | 0.157 | 4.951 | 5.686 | < 0.001 |
| 45–49 | 8.763 | 0.122 | 8.524 | 9.002 | < 0.001 | 8.311 | 0.152 | 8.013 | 8.610 | < 0.001 |
| 50–54 | 8.329 | 0.125 | 8.083 | 8.575 | < 0.001 | 7.782 | 0.158 | 7.473 | 8.091 | < 0.001 |
| 55–59 | 10.700 | 0.123 | 10.459 | 10.940 | < 0.001 | 10.171 | 0.154 | 9.87 | 10.472 | < 0.001 |
| 60–64 | 9.476 | 0.134 | 9.213 | 9.739 | < 0.001 | 9.010 | 0.171 | 8.675 | 9.345 | < 0.001 |
| 65–69 | 11.203 | 0.139 | 10.930 | 11.476 | < 0.001 | 10.589 | 0.175 | 10.246 | 10.933 | < 0.001 |
| 70–74 | 11.546 | 0.171 | 11.210 | 11.882 | < 0.001 | 11.255 | 0.194 | 10.876 | 11.635 | < 0.001 |
| 75–79 | 13.387 | 0.200 | 12.995 | 13.779 | < 0.001 | 13.086 | 0.212 | 12.67 | 13.503 | < 0.001 |

**Sex (%)**

| Male | Refer | Refer | Refer |
| Female | 2.53 | 0.074 | 2.384 | 2.676 | < 0.001 | 2.584 | 0.093 | 2.401 | 2.767 | < 0.001 |

**History of CVD (%)**

| No | Refer | Refer | Refer |
| Yes | 0.085 | 0.064 | −0.041 | 0.212 | 0.186 | 0.184 | 0.083 | 0.348 | 0.027 |

**History of diabetes (%)**

| No | Refer | Refer | Refer |
| Yes | 0.075 | 0.079 | −0.078 | 0.229 | 0.661 | −0.02 | 0.097 | −0.21 | 0.169 | 0.834 |

**History of hyperlipidemia (%)**

| No | Refer | Refer | Refer |
| Yes | 0.652 | 0.123 | 0.411 | 0.892 | 0.892 | 0.716 | 0.151 | 0.419 | 1.013 | < 0.001 |

**BMI group (%)**

| 18.5–25 | Refer | Refer | Refer |
| < 18.5 | 1.149 | 0.166 | 0.824 | 1.474 | < 0.001 | 1.052 | 0.225 | 0.610 | 1.494 | < 0.001 |
| 25–30 | 2.317 | 0.172 | 1.980 | 2.654 | < 0.001 | 1.868 | 0.234 | 1.409 | 2.327 | < 0.001 |
| > 30 | 3.065 | 0.213 | 2.647 | 3.483 | < 0.001 | 2.208 | 0.281 | 1.657 | 2.760 | < 0.001 |

**High risk drinking (%)**

| No | Refer | Refer | Refer |
| Yes | −0.205 | 0.108 | −0.416 | 0.006 | 0.057 | −0.186 | 0.139 | −0.459 | 0.086 | 0.180 |

**Physical activity (%)**

| Not regular | Refer | Refer | Refer |
| Regular | −0.096 | 0.070 | −0.232 | 0.041 | 0.170 | 0.014 | 0.104 | −0.189 | 0.218 | 0.889 |

**Diabetes (%)**

| No | Refer | Refer | Refer |
| Yes | −0.215 | 0.122 | −0.453 | 0.023 | 0.077 | 0.320 | 0.151 | 0.024 | 0.615 | 0.034 |

### Parameters

| Parameters | Lead (μg/dL) |  |  |  | Mercury (μg/L) |  |  |  |
|------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|            | β | SE | 95% CI | p-value | β | SE | 95% CI | p-value |
|            | Adjusted R² | 0.773, p < 0.001 |  |  | Adjusted R² | 0.773, p < 0.001 |  |  |

**(B) For lead and mercury**

| Serum lead or mercury | 0.104 | 0.056 | 0.016 | 0.214 | 0.044 | 0.110 | 0.036 | 0.039 | 0.181 | 0.003 |
| Serum cotinine (ng/mL) | 0.0002 | 0.00005 | 0.0001 | 0.0003 | < 0.001 | 0.0002 | 0.00005 | 0.0001 | 0.0003 | < 0.001 |

**Age group (%)**

| 20–34 | Refer | Refer | Refer |
| 35–39 | 5.376 | 0.113 | 5.154 | 5.598 | < 0.001 | 5.365 | 0.113 | 5.143 | 5.586 | < 0.001 |
| 40–44 | 5.509 | 0.117 | 5.280 | 5.738 | < 0.001 | 5.502 | 0.116 | 5.275 | 5.730 | < 0.001 |
| 45–49 | 8.837 | 0.117 | 8.607 | 9.067 | < 0.001 | 8.836 | 0.116 | 8.608 | 9.064 | < 0.001 |
| 50–54 | 8.406 | 0.121 | 8.169 | 8.643 | < 0.001 | 8.409 | 0.118 | 8.177 | 8.642 | < 0.001 |
| 55–59 | 10.765 | 0.120 | 10.531 | 11.000 | < 0.001 | 10.782 | 0.116 | 10.556 | 11.009 | < 0.001 |
| 60–64 | 9.555 | 0.130 | 9.301 | 9.810 | < 0.001 | 9.577 | 0.126 | 9.330 | 9.824 | < 0.001 |

Continued
(LODs) for lead, mercury, and cadmium were 0.223 µg/dL, 0.05 µg/L, and 0.087 µg/L, respectively. No sample had a value of below a LOD. For internal quality assurance and control, commercial standards (Lyphochek Whole Blood Metals, Bio-Rad, CA, USA) were used as reference materials.

**Urinary cotinine and smoking verification.** Spot urinary samples were collected for a quantity of urinary cotinine by gas chromatography and mass spectrometry using PerkinElmer Clarus 600 T, with a detection limit of 1.26 ng/ml. Standard reference materials have been used for internal quality assurance and control purposes (ClinChek, RECIPE, Munich, Germany). The G-EQUAS uses a standard protocol to measure urinary cotinine. Subjects with urinary cotinine ≥ 50 ng/mL were defined as cotinine-verified smokers52,53.

**Laboratory measurements.** Information on age, education, smoking history, and alcohol intake was collected during medical checkups using the standard procedure. Height and weight measurements were performed with the participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumstance (cm) was measured at the midpoint between the bottom of the rib cage and the iliac crest of the mid-axillary line when exhaling. Blood pressure was measured with the participants in a seated position following a 5-min rest period. Blood pressure was measured in the right arm on three occasions using a mercury sphygmomanometer and was averaged to determine the final blood pressure reading. Blood samples were collected in the morning after an overnight fast. Serum concentrations of high-density lipoprotein cholesterol (HDL-C), triglycerides, alanine aspartate aminotransferase (ALT), aspartate aminotransferase (AST), and glucose were measured using an automatic analyzer (Hitachi 7600; Hitachi, Tokyo, Japan). Serum low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation: serum LDL-C = serum total cholesterol–serum HDL-C–serum triglyceride/5. hs-CRP level was measured with immunoturbidimetry using the Cobas 8000 (Roche, Mannheim, Germany). All clinical analyses were performed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare.

**Table 4.** The relationship between the levels of serum cadmium, lead, mercury and hs-CRP and 10-year risk of CVD by multiple regression.

| Parameters | Lead (µg/dL) | Mercury (µg/L) |
|------------|--------------|----------------|
|            | β | SE | 95% CI | p-value | β | SE | 95% CI | p-value |
| Adjusted R² = 0.773, p < 0.001 | Adjusted R² = 0.773, p < 0.001 |
| 65–69 | 11.288 | 0.134 | 11.025 | 11.551 | < 0.001 | 11.322 | 0.13 | 11.067 | 11.578 | < 0.001 |
| 70–74 | 11.630 | 0.167 | 11.302 | 11.958 | < 0.001 | 11.671 | 0.164 | 11.349 | 11.993 | < 0.001 |
| 75–79 | 13.484 | 0.195 | 13.101 | 13.867 | < 0.001 | 13.524 | 0.193 | 13.146 | 13.903 | < 0.001 |

Sex (%)

| Male | Refer | Refer | Refer |
|------|-------|-------|-------|
| female | 2.641 | 0.074 | 2.496 | 2.787 | < 0.001 | 2.661 | 0.074 | 2.517 | 2.805 | < 0.001 |

History of CVD (%)

| No | Refer | Refer |
|----|-------|-------|
| Yes | 0.087 | 0.065 | − 0.039 | 0.213 | 0.177 | 0.083 | 0.064 | − 0.043 | 0.209 | 0.199 |

History of diabetes (%)

| No | Refer | Refer |
|----|-------|-------|
| Yes | 0.075 | 0.079 | − 0.079 | 0.229 | 0.339 | 0.070 | 0.079 | − 0.083 | 0.224 | 0.369 |

History of hyperlipidemia (%)

| No | Refer | Refer | Refer |
|----|-------|-------|-------|
| Yes | 0.656 | 0.123 | 0.416 | 0.897 | < 0.001 | 0.657 | 0.123 | 0.417 | 0.897 | < 0.001 |

BMI group (%)

| 18.5–25 | Refer | Refer |
|< 18.5 | 1.142 | .166 | .816 | 1.467 | < 0.001 | 1.134 | 0.166 | 0.808 | 1.459 | < 0.001 |
| 25–30 | 2.315 | .172 | 1.978 | 2.653 | < 0.001 | 2.292 | 0.172 | 1.954 | 2.630 | < 0.001 |
| > 30 | 3.069 | .213 | 2.65 | 3.487 | < 0.001 | 3.028 | 0.214 | 2.609 | 3.447 | < 0.001 |

High risk drinking (%)

| No | Refer | Refer |
|----|-------|-------|
| Yes | − 0.221 | 0.108 | − 0.433 | − 0.009 | 0.041 | − 0.228 | 0.108 | − 0.440 | − 0.017 | 0.035 |

Physical activity (%)

| Not regular | Refer | Refer |
| Regular | − 0.101 | 0.070 | − 0.238 | 0.036 | 0.147 | − 0.101 | 0.070 | − 0.238 | 0.036 | 0.147 |

Diabetes (%)

| No | Refer | Refer |
|----|-------|-------|
| Yes | − 0.216 | 0.122 | − 0.454 | 0.023 | 0.076 | − 0.210 | 0.122 | − 0.448 | 0.028 | 0.084 |
Parameters. Alcohol intakes were categorized as low or high-risk drinking (high-risk drinking was defined as >5 drinks per day and ≥ 1 month). Physical activity has been dichotomized as regular or irregular. Regular physical activity was defined as: (1) participation in vigorous physical activity (running, fast cycling, climbing, football, fast swimming, basketball, squash, singles tennis, rope jumping or occupational or recreational activity involving the carrying of heavy objects), ≥ 20 min per session ≥ 3 days per week (2) or participation in moderate physical activity (slow swimming, volleyball, doubles tennis, or occupational or recreational activity involving the carrying of light objects); ≥ 30 min per session ≥ 5 days per week54.

Assessment of nutrient intake. All participants were required to maintain their usual dietary habits before collecting data on dietary intake. Daily food intake was measured using the 24-h recall method, and nutrient intake was calculated using the Can-Pro 3.0 nutrient intake assessment software developed by the Korean Nutrition Society3.

Framingham estimate of 10-year coronary heart disease (CVD) risk. The Framingham risk equation was used for the estimation of 10-year CVD risk for each participant. The Framingham estimate of 10-year risk of CVD was derived from the Framingham point score, based on HDL cholesterol, total cholesterol concentrations, age, systolic blood pressure, and smoking by gender. The total risk factors ranged from 0–17 in males and 1–25 in females, representing Framingham point scores ranging from 1 to 30%17. They are categorized as low risk, <10%; intermediate-risk, 10%–19%; and high risk, ≥ 20%55.

Statistical analysis. All statistical analyses were undertaken using STATA software (version 16.0; StataCorp, Texas, USA). The baseline characteristics of participants were summarized using frequency and proportion for categorical variables; mean and standard deviation for continuous variables.

Pearson’s correlation coefficient was calculated for checking the relationships between levels of serum heavy metals and cardiometabolic risk factors, dietary intake. To define different levels of serum cadmium, lead, mercury, and hs-CRP, we categorized them into quartiles. We compared the mean values of cardiometabolic risk factors according to the quartiles of serum cadmium, lead, mercury, and hs-CRP using ANOVA (one-way) OR or Mann–Whitney test was performed independently for each variable.

Figure 3. The marginal effect of the levels of serum lead, cadmium, mercury and hs-CRP on the 10-year risk of CVD by age group among the Korean population.
The serum heavy metals (cadmium, lead, mercury, and hs-CRP) levels were log2-transformed because their distribution was right skewed. The serum heavy metal levels were described as the geometric mean (GM) and 95% confidence interval (CI).

A multiple regression analysis was used to analyze the associations between the blood heavy metal levels and 10-year risk of CVDs. The regression analyses were adjusted for serum cotinine (ng/mL), age group (20–34, 35–39, 40–44, 45–49, 50–59, 60–64, 65–69, 70–74, 75–79), sex (males, females), high-risk drinking (yes, no), physical activity (not regular, regular), BMI groups (<18.5, ≥18.5 and ≤25, >25 and <30, ≥30), family history of CVDs, or diabetes or dyslipidemia (yes, no), and type 2 diabetes. The marginal effects were then used to predict the 10-year risk of CVD. Statistical tests were two-sided, p-value <0.05 was considered statistically significant.

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Author contributions

Study concept and design (H.N.D.); acquisition of data (H.N.D. and M.S.K., H.O., N.H.M.H.); analysis and interpretation of data (H.N.D. and M.S.K.); statistical analysis (H.N.D.) drafting of the manuscript (H.N.D. and M.S.K.).

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Competing interests

The authors declare no competing interests.

Additional information

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