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Environmental Exposures to Lead, Mercury, and Cadmium and Hearing Loss in Adults and Adolescents: KNHANES 2010–2012

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Background: The prevalence of hearing loss increases rapidly with aging. Hearing loss is common in all age groups, even in young adults and adolescents. A growing body of evidence has suggested that heavy metals have ototoxic effects, yet few epidemiological studies have investigated the association between heavy metals and hearing loss in a general population that includes adults and adolescents.

Objectives: We examined the association between environmental exposures to lead, mercury, and cadmium and the risk of hearing loss in adults and adolescents while controlling for potential confounding factors, including noise exposures and clinical factors.

Methods: We analyzed cross-sectional data from 5,187 adults and 853 adolescents in the Korean National Health and Nutrition Examination Survey 2010–2012. Pure-tone average (PTA) of hearing thresholds at high frequency (3, 4, and 6 kHz) were computed, and hearing loss was defined as a PTA >25 dB in adults and PTA >15 dB in adolescents.

Results: In adults, the highest (vs. lowest) quartiles of blood lead and cadmium were associated with 1.70 (95% CI: 1.25, 2.31) and 1.47 (95% CI: 1.05, 2.05) odds ratios for high-frequency hearing loss (p-trend <0.001 and = 0.007), respectively. In adolescents, the highest quartile (vs. lowest) of blood cadmium had an odds ratio of 3.03 (95% CI: 1.44, 6.40) for high-frequency hearing loss (p-trend = 0.003), but blood lead was not associated with hearing loss. No significant association between blood mercury and hearing loss was suggested in either adults or adolescents.

Conclusions: The results of the present study suggest that exposure to environmental lead and cadmium in adults and exposure to environmental cadmium in adolescents may play a role in the risk of hearing loss. https://doi.org/10.1289/EHP565

Introduction

Hearing loss is a commonly experienced chronic disorder throughout the world. Although hearing loss is common even in young adults and school-age children, it is highly prevalent in older adults (Agrawal et al. 2008; Shargorodsky et al. 2010). Hearing loss can affect communication and can therefore lead to a reduced quality of life and to a loss in economic activity (Agrawal et al. 2008). In adolescents, even slight hearing loss can lead to poor development of communication skills and psychological function and can thus lower educational achievement (Anderson 1992; Northern and Down 2002).

A growing body of evidence from *in vitro* and animal studies has demonstrated ototoxic effects of lead, cadmium, and mercury; possible underlying mechanisms of their ototoxic effects include oxidative stress through depletion of glutathione and protein-bound sulfhydryl groups and related reductions in blood flow and lipid peroxidation in the cochlea, leading to latency in auditory nerve conduction and to an elevation of auditory thresholds (Park 2015; Prasher 2009). Although high exposure to heavy metals, particularly to lead, in occupational settings and hearing loss has been studied, little is known about the ototoxic effects of long-term exposure to low-level metals in the general population of adults and adolescents. With regard to lead, a few studies of low-level exposure and hearing loss have been conducted in U.S. older men (Park et al. 2010), general adults (Choi et al. 2012a), and adolescents (Shargorodsky et al. 2011); for cadmium, one cross-sectional study in U.S. general adults (Choi et al. 2012a) and one cross-sectional study in U.S. adolescents (Shargorodsky et al. 2011) have been conducted; for mercury, one cross-sectional study was conducted in U.S. general adolescents, but it failed to observe a significant association (Shargorodsky et al. 2011) despite the biological plausibility of mercury affecting the auditory brainstem response (Murata et al. 1999). Although exposure to lead, cadmium, and mercury has decreased considerably in many countries, these heavy metals continue to be widely used in a variety of consumer products, and environmental exposure to cadmium and mercury is known to be particularly high in Asian Pacific people, including Koreans, because of dietary exposure via consumption of contaminated food: for example, rice, fish, and shellfish (Park and Lee 2013a, 2013b). However, no epidemiologic studies have examined the association between environmental exposures to heavy metals and hearing loss in the Korean general population.

In the present study, we examined the association between environmental heavy metal exposure and risk of hearing loss in adults and adolescents using data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2012 while controlling for potential confounding factors including various noise exposures and clinical risk factors.

Methods

Study Population

The KNHANES, conducted by the Korea Center for Disease Control and Prevention (KCDC) since 1998, is an ongoing series of cross-sectional surveys designed to determine health and nutrition states in a representative Korean population. The surveys consist of three sections: Health and Behavior Interview, Health Examination, and Nutrition Survey. KNHANES is a publicly available data set. Because audiometric examination and blood metal measurements were conducted in KNHANES 2008–2012 and information on detailed noise exposures, an important

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confounding factor, was available in KNHANES 2010–2012 (KCDC 2014), the present analysis included data from three years of KNHANES V data for 2010–2012. Based on the 2009 National Census Registry, 192 sampling units (3,800 households) per year were randomly selected for the KNHANES 2010–2012, and approximately 80% of participants completed the health examination survey (8,958 in 2010; 8,518 in 2011; 8,057 in 2012) (KCDC 2014). In each survey year, 2,400 participants ≥ 10 y old were randomly selected for blood measurements of lead, mercury, and cadmium. In KNHANES 2010–2012, subjects ≥ 12 y old were selected to participate in the audiometric examination component, which resulted in 6,394 total subjects available for analysis (5,515 adults 20–87 y old and 879 adolescents 12–19 y old). A total of 354 participants (328 adults and 26 adolescents) had missing data on covariates and were excluded from the analysis (further details are available in the Supplemental Material, "Study Population"), leaving 6,040 participants (5,187 adults and 853 adolescents). Excluded participants were not statistically different from included participants in terms of demographic and clinical factors. The Institutional Review Board of the KCDC approved the study (IRB No. 2010-02CON-21C in 2010; 2011-02CON-06-C in 2011; 2012-01EXP-01-2C in 2012), and all participants provided written informed consent.

Audiometric Measures

The KNHANES audiometric examination was performed in a sound-isolated room (model SAD800; Earologic Inc., SonTek) by otorhinolaryngology-resident physicians using an audiometer (model SA203; Central Medics Inc., Sweden) according to the procedure standardized by the Korean Society of Otorhinolaryngology–Head and Neck Surgery [Korea Centers for Disease Control and Prevention (KCDC) 2012]. Pure-tone air conduction hearing thresholds were obtained for each ear at frequencies of 0.5, 1, 2, 3, 4, and 6 kHz over an intensity range of -10 to 110 dB. We computed pure-tone average (PTA) at speech frequencies (0.5, 1, 2, and 4 kHz; speech-PTA) and high frequencies (3, 4, and 6 kHz; high-PTA) (Agrawal et al. 2008; Choi et al. 2012b). The distributions of these PTAs were normal. Adult hearing loss was defined as a PTA >25 dB in either ear [World Health Organization/International Repository for Information Sharing (Informal Working Group on Prevention of Deafness and Hearing Impairment Programme Planning) 1991]. Because adolescents have greater hearing sensitivity, adolescent hearing loss was defined as a PTA >15 dB in either ear (Niskar et al. 1998; Shargorodsky et al. 2010).

Determination of Lead, Mercury, and Cadmium in Blood

Blood samples for lead, mercury, and cadmium measurements were drawn into trace-metal-free ethylenediaminetetraacetic acid (EDTA) tubes, and specimens were immediately transferred at 2–8°C to a central laboratory for analysis (NeoDin Medical Institute, Seoul, Korea). Lead and cadmium concentrations in venous whole blood were measured using graphite furnace atomic absorption spectrometry (model AAnalyst 600; PerkinElmer, Finland); blood mercury concentrations were measured using a direct mercury analyzer and a gold amalgam method (model DMA-80; Milestone, Italy) (KCDC 2014). The limits of detection (LODs) were 0.12 μg/dL, 0.158 μg/L, and 0.056 μg/L for blood lead, mercury, and cadmium, respectively. None of the adult samples exhibited values below the LOD, and only 2 (0.2%) adolescent samples had blood cadmium below the LOD. For internal quality assurance and control, commercial standard reference materials were obtained from Bio-Rad (Lyphochek® Whole Blood Metals Control; Bio-Rad, Hercules, CA, USA). Interassay coefficients of variation (CV) ranged from 0.58% to 5.52% for the blood lead quality control (QC) pools, from 0.97% to 7.78% for the blood mercury QC pools, and from 0.97% to 7.78% for the blood cadmium QC pools (KCDC 2011). The NeoDin Medical Institute has a certified license from the Korean Ministry of Labor for external quality control of heavy metals laboratory analyses and has passed the German External Quality Assessment Scheme, the U.S. CDC program, and the Korea Occupational Safety and Health Administration (Korea OSHA) program.

Covariates

We considered age, sex, education, household income, cigarette smoking, body mass index (BMI), diabetes, hypertension, and noise exposures (e.g., occupational, firearm, recreational noise) as potential confounders (Choi et al. 2012a). Education was categorized as elementary school or less (reference), middle school graduation, high school graduation, and college or more. Household income was available as quartiles each survey year. History of cigarette smoking was categorized as self-reported current smoker, former smoker, or nonsmoker (reference). BMI was calculated by dividing the measured weight in kilograms by the measured height in meters squared (continuous). Current hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication (KCDC 2014). Current diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL, self-reported physician diagnosis, or self-reported use of medication (oral hypoglycemic treatment or insulin injection) (KCDC 2014). Noise exposures were based on self-report (vs. nonexposure). Exposure to occupational noise was defined as "if the subject had ever worked in places exposed to loud noise (e.g., generator and mechanical noise) for three months or more." Exposure to recreational noise was defined as "if the subject had ever listened to music by using earphones in noisy places such as a subway or bus" or "if the subject had ever been exposed to loud noise outside of work (e.g., power tools or loud music)." Exposure to firearm noise was defined as "if the subject had ever been exposed to instantaneous loud noise such as explosions and gunfire."

Occupational noise, diabetes, and hypertension were not included as confounders in multivariable models for adolescents because the number of subjects who were exposed to occupational noise was too small for a reliable statistical analysis ($n = 6$), and information on adolescent diabetes and hypertension was not available in the KNHANES.

In adults, the urinary cotinine level, dietary fish intake, and total cholesterol were also considered as potential confounders. Urinary cotinine concentrations, a biomarker of exposure to active and passive tobacco smoke, were measured using gas chromatography mass spectrometry (model Clarus 600T; PerkinElmer, Finland), and the data are available in KNHANES 2010–2011 ($n = 3{,}292$) (KCDC 2014). Dietary fish and shellfish intake, a major route for mercury exposure and omega-3 intake (Raimann et al. 2014), was estimated by food frequency questionnaire (FFQ) interviews available in a randomly selected subset ($n = 2{,}973$). Daily fish intake was estimated as the sum of daily intake frequencies of nine fish items (mackerel, tuna, yellow corbina, pollack, anchovy, fish pastes, squid, shellfish, and pickled fish) available in the KNHANES FFQ. We first computed the daily intake frequency for each fish item (range from 0 to 2 per day; e.g., 2 times per week was converted to 0.29 times per day) and then summed the overall intake scores ($0 \leq$ scale ≤ 18) for these 9 items.

Statistical Analyses

We performed all statistical analyses using SAS survey procedures (version 9.4; SAS Institute Inc.) to account for the complex sampling design and weights in KNHANES 2010–2012. For our analyses, we used 3-y weights for individual probabilities drawn from the blood heavy metals data set and the audiometric examination data set according to the KNHANES analysis tutorial (KCDC 2014). Adults and adolescents were analyzed separately because adults and adolescents may have different susceptibility to heavy metals–induced hearing loss.

The distributions of blood lead, mercury, and cadmium were right skewed and were natural log–transformed before the analyses. Logistic regression models (PROC SURVEYLOGISTIC) were used to estimate odds ratios (ORs) of hearing loss associated with blood lead, mercury, and cadmium levels (as log-transformed or as quartiles). We constructed single- and multi- (all three) pollutant models based on lead, mercury, and cadmium and observed potential attenuation of a single-pollutant effect of each pollutant by adjusting for copollutants. All models in adults were adjusted for age; age squared (age^2); sex; education; BMI; current cigarette smoking; current diagnosis of hypertension and diabetes; and occupational, recreational, and firearm noise exposures. We fit age and age^2 to capture nonlinear effects of age. For the analyses of the adolescents, occupational noise, diabetes, and hypertension were not included. Linear regression models (PROC SURVEYREG) were used to evaluate the association between blood lead, mercury, and cadmium with hearing thresholds in PTA as continuous outcome.

Sensitivity analysis. Sensitivity analyses for different multivariate models and stratified models were conducted to test whether our results were robust to various alternative modeling. First, we examined logistic regression models using speech-frequency PTA with different frequency sets (0.5, 1, and 2 kHz) used by Shargorodsky et al. (2010, 2011). High-frequency PTA with different frequency sets [3, 4, 6, and 8 kHz; also suggested by Shargorodsky et al. (2010, 2011)] was not examined owing to the lack of available data for 8 kHz in the KNHANES. Second, we examined whether the results differed after further adjustment for urinary cotinine (continuous, log-transformed to normalize), total blood cholesterol (continuous, log-transformed to normalize), and fish and shellfish intake (quartiles). Third, we examined whether the results differed after excluding adjustment for education. Fourth, we conducted sensitivity analyses stratified by adult age groups.

Results

A total of 5,187 Korean adults [mean ± the standard error of the mean (±SE)]: 45.5 ± 0.30 years of age) and 853 adolescents (15.6 ± 0.10 years of age) had available data for the analysis. Approximately 22.6% and 41.2% of adults and 5.7% and 12.7% of adolescents had speech-frequency and high-frequency hearing loss, respectively. Participant characteristics and distributions of blood lead, mercury, and cadmium are presented in Table 1 (adults) and Table 2 (adolescents).

Among adults, age-adjusted geometric means of blood lead, mercury, and cadmium were 2.12 [95% confidence interval (CI): 2.08, 2.15 μg/dL], 3.58 (95% CI: 3.48, 3.68) μg/L, and 1.00 (95% CI: 0.98, 1.02) μg/L, respectively. Each level of blood lead, mercury, or cadmium was likely to be higher in smokers (vs. nonsmokers) and in adults who were older and was significantly different depending on sex, household income, and firearm noise exposure. Additionally, blood lead levels were higher in individuals with high-frequency hearing loss, BMI ≥ 25 kg/m^2, and with occupational noise exposure. Blood mercury levels were higher in individuals who were more educated, with BMI ≥ 25 kg/m^2, with occupational noise exposure, and without speech-frequency hearing loss. Blood cadmium levels were higher in those without speech-frequency hearing loss, diabetes, and recreational noise exposure.

Among adolescents, age-adjusted geometric means of blood lead, mercury, and cadmium were 1.26 (95% CI: 1.22, 1.30) μg/dL, 2.03 (95% CI: 1.96, 2.12) μg/L, and 0.36 (95% CI: 0.34, 0.38) μg/L, respectively. Blood lead levels were higher in males and in adolescent smokers; blood mercury levels were higher in males and in adolescents with BMI ≥ 25 kg/m^2; blood cadmium levels were higher in adolescents with high-frequency hearing loss and lower household income and in adolescent smokers.

Table 3 and Table S1 (extended table of Table 3) show logistic regression results for the risk of hearing loss (speech and high PTA > 25dB) with blood lead, mercury, and cadmium using single- and multi-pollutant models among adults. After adjusting for potential confounders, blood lead and cadmium, as both continuous variables and as quartiles, were significantly associated with increased odds of high-frequency hearing loss in single- and multi-pollutant models. Fully adjusted ORs for high-frequency hearing loss comparing the highest versus the lowest blood lead and cadmium quartiles were 1.70 (95% CI: 1.25, 2.31) and 1.47 (95% CI: 1.05, 2.05) respectively, in single-pollutant models (p for trend < 0.001 and = 0.007). Speech-frequency hearing loss was associated with blood lead with borderline significance. No significant associations of blood mercury with hearing loss were found. Linear regression results for hearing thresholds (decibels) are presented in Table S2. Blood lead, as both continuous variables and as quartiles, was significantly associated with higher (poorer) speech-frequency PTA and high-frequency PTA, respectively.

Table 4 and Table S3 (extended table of Table 4) present logistic regression results for adolescents. Blood cadmium, as both continuous variables and as quartiles, was significantly associated with increased odds of high-frequency hearing loss in single- and multi-pollutant models. Adolescents in the highest cadmium quartile (vs. the lowest) had OR = 3.03 (95% CI: 1.44, 6.40) for high-frequency hearing loss in single-pollutant models (p for trend = 0.003). In addition, blood cadmium was associated with speech-frequency hearing loss with borderline significance. No significant associations of blood mercury with hearing loss were found in adolescents. The results of the linear regression showed that blood lead, as continuous variables and as quartiles, had significant associations with high-frequency PTA (see Table S4).

When we examined all analyses for speech-frequency hearing loss using different frequency sets (0.5, 1, and 2 kHz), we found that the results were consistent with those using the original frequency sets (0.5, 1, 2, and 4 kHz) (data not shown).

We performed sensitivity analyses stratified by adult age groups. Participants who were 40–59 y old and 60–87 y old showed stronger dose-dependent associations of high-frequency hearing loss with blood lead levels, but participants 20–39 y old showed no significant associations (p for interaction by age = 0.041, Table S5).

We performed another sensitivity analysis in adults after additional adjustment for urinary cotinine (a biomarker of active and passive cigarette smoking), dietary fish intake [a major source of mercury exposure and known to share sources of omega-3 fatty acids that may have protective effects on hearing loss (Gopinath et al. 2010)], and total blood cholesterol levels (a potential risk factor for hearing loss). We found that associations of hearing loss with blood cadmium remained unchanged after adjusting for cotinine (Table S6), and associations with blood mercury remained nonsignificant even after adjusting for fish intake

Table 1. Age-adjusted geometric means [95% confidence intervals (CIs)] of blood lead, mercury, and cadmium by participant characteristics in adults.

Variables	No. (%) of participants	Blood lead		Blood mercury		Blood cadmium	
		μg/dL (95% CI)	*p*-Value	μg/L (95% CI)	*p*-Value	μg/L (95% CI)	*p*-Value
Total	5,187	2.12 (2.08, 2.15)		3.58 (3.48, 3.68)		1.00 (0.98, 1.02)	
Hearing loss (>25 dB) at speech frequency[a]							
No	4,063 (77.4)	2.12 (2.09, 2.16)		3.66 (3.56, 3.77)		1.02 (0.99, 1.04)	
Yes	1,124 (22.6)	2.10 (2.02, 2.18)	0.574	3.30 (3.09, 3.51)	0.002	0.94 (0.90, 0.98)	<0.001
Hearing loss (>25 dB) at high frequency[b]							
No	3,094 (58.8)	2.07 (2.03, 2.11)		3.60 (3.50, 3.70)		1.01 (0.93, 1.03)	
Yes	2,093 (41.2)	2.19 (2.13, 2.25)	<0.001	3.55 (3.39, 3.72)	0.593	0.98 (0.95, 1.01)	0.163
Sex							
Male	2,548 (49.3)	2.50 (2.45, 2.54)		4.27 (4.12, 4.42)		0.92 (0.90, 0.95)	
Female	2,639 (50.7)	1.80 (1.76, 1.84)	<0.001	3.01 (2.91, 3.11)	<0.001	1.07 (1.05, 1.10)	<0.001
Age (years)							
20,39	2,031 (39.4)	1.80 (1.76, 1.84)		3.25 (3.15, 3.35)		0.75 (0.73, 0.77)	
40,59	2,101 (40.3)	2.34 (2.29, 2.39)		4.06 (3.92, 4.20)		1.19 (1.16, 1.22)	
60,87	1,055 (20.3)	2.40 (2.31, 2.50)	<0.001	3.37 (3.14, 3.62)	0.009	1.23 (1.18, 1.29)	<0.001
Household income							
Low	1,290 (27.0)	2.20 (2.14, 2.26)		3.34 (3.17, 3.52)		1.06 (1.02, 1.11)	
Low-middle	1,314 (25.3)	2.12 (2.06, 2.17)		3.49 (3.32, 3.66)		0.99 (0.95, 1.03)	
High-middle	1,263 (24.7)	2.04 (1.97, 2.11)		3.54 (3.38, 3.71)		0.96 (0.92, 1.00)	
High	1,320 (23.0)	2.10 (2.04, 2.17)	0.006	4.02 (3.83, 4.21)	<0.001	0.98 (0.94, 1.02)	0.003
Education							
≤Elementary school	854 (18.7)	1.95 (1.87, 2.03)		2.89 (2.68, 3.12)		0.95 (0.91, 1.00)	
Middle school	541 (10.6)	2.28 (2.18, 2.38)		3.83 (3.58, 4.10)		1.07 (1.02, 1.13)	
High school	1,932 (38.9)	2.16 (2.12, 2.22)		3.59 (3.46, 3.72)		1.04 (1.00, 1.07)	
≥College	1,860 (31.8)	2.11 (2.07, 2.15)	0.010	3.94 (3.80, 4.08)	<0.001	0.95 (0.93, 0.98)	0.647
Body mass index (kg/m^2)							
<25	3,492 (67.2)	2.09 (2.05, 2.13)		3.36 (3.25, 3.47)		1.00 (0.97, 1.02)	
≥25	1,695 (32.8)	2.18 (2.12, 2.23)	0.009	4.07 (3.90, 4.24)	<0.001	1.00 (0.97, 1.03)	0.877
Hypertension							
No	3,833 (73.1)	2.12 (2.09, 2.16)		3.57 (3.47, 3.67)		1.00 (0.98, 1.02)	
Yes	1,354 (26.9)	2.10 (2.03, 2.17)	0.585	3.60 (3.39, 3.82)	0.785	0.98 (0.94, 1.02)	0.320
Diabetes mellitus							
No	4,767 (91.9)	2.13 (2.10, 2.16)		3.59 (3.50, 3.69)		1.00 (0.98, 1.03)	
Yes	420 (8.1)	2.01 (1.89, 2.14)	0.079	3.40 (3.07, 3.76)	0.275	0.91 (0.85, 0.97)	0.006
Cigarette smoking							
Never smoker	3,000 (57.3)	1.87 (1.83, 1.90)		3.15 (3.04, 3.25)		0.96 (0.94, 0.99)	
Former smoker	940 (17.7)	2.31 (2.24, 2.39)		4.09 (3.87, 4.34)		0.80 (0.77, 0.83)	
Current smoker	1,247 (25.0)	2.65 (2.59, 2.72)	<0.001	4.36 (4.16, 4.57)	<0.001	1.26 (1.22, 1.30)	<0.001
Occupational noise exposure							
No	4,525 (86.6)	2.07 (2.04, 2.11)		3.53 (3.43, 3.64)		0.99 (0.97, 1.01)	
Yes	662 (13.4)	2.42 (2.33, 2.52)	<0.001	3.87 (3.60, 4.15)	0.019	1.02 (0.97, 1.07)	0.347
Recreational noise exposure							
No	4,469 (86.0)	2.13 (2.09, 2.16)		3.60 (3.49, 3.71)		1.01 (0.99, 1.03)	
Yes	718 (14.0)	2.07 (2.00, 2.13)	0.111	3.44 (3.26, 3.64)	0.156	0.91 (0.86, 0.95)	<0.001
Firearm noise exposure							
No	3,980 (75.9)	2.03 (1.99, 2.07)		3.40 (3.30, 3.51)		1.02 (1.00, 1.04)	
Yes	1,207 (24.1)	2.42 (2.35, 2.49)	<0.001	4.19 (3.98, 4.41)	<0.001	0.94 (0.90, 0.97)	<0.001

Note: Age adjusted except for age groups, which are presented as the unadjusted blood lead, mercury, and cadmium. *p*-Value based on survey *t*-test for binominal groups and based on Wald test for categorical groups. Weighted percentages based on survey frequency.
[a]Pure tone average at 0.5, 1, 2, and 4 kHz.
[b]Pure tone average at 3, 4, and 6 kHz.

(Table S7). Because cotinine measures were obtained only in the first two years of the three-year period of KNHANES V (i.e., in 2010–2011 but not in 2012) and dietary intakes were available only in a subset of KNHANES 2010–2012, the sample size for these analyses was small. Associations of hearing loss with blood lead, mercury, and cadmium remained unchanged after adjusting for total cholesterol (Table S8).

Moreover, we conducted sensitivity analyses in adults after excluding adjustment for education. Associations of hearing loss with blood lead, mercury, and cadmium after adjustment for education were less significant than those excluding for education (Table S9).

Discussion

This is the first study of associations between heavy metals and hearing loss evaluated simultaneously in adults and adolescents. In our analysis of a representative sample of Korean adults and adolescents who participated in the KNHANES 2010–2012, higher exposure to lead and cadmium were significantly associated with high-frequency hearing loss in adults, even after adjustment for potential confounding factors including various noise exposures and clinical risk factors. We also found a significant association between blood cadmium and hearing loss in adolescents. In addition, we found that the observed associations in single-pollutant models were slightly attenuated in multi-pollutant models, suggesting that confounding by copollutants is minimal. No significant association between blood mercury and hearing loss was observed in either adults or adolescents.

In adults, the highest quartiles of blood cadmium (1.47 – 6.42 μg/L) and blood lead (2.82 – 26.51 μg/dL) presented ORs of 1.47 (95% CI: 1.05, 2.05) and 1.70 (95% CI: 1.25, 2.31) for high-

Table 2. Age-adjusted geometric means [95% confidence intervals (CIs)] of blood lead, mercury, and cadmium by participant characteristics in adolescents.

Variables	No. (%) of participants	Blood lead		Blood mercury		Blood cadmium	
		μg/dL (95% CI)	*p*-Value	μg/L (95% CI)	*p*-Value	μg/L (95% CI)	*p*-Value
Total	853	1.26 (1.22, 1.30)		2.03 (1.96, 2.12)		0.36 (0.34, 0.38)	
Hearing loss (>15 dB) at speech frequency[a]							
No	805 (94.3)	1.26 (1.22, 1.30)		2.03 (1.95, 2.12)		0.36 (0.34, 0.38)	
Yes	48 (5.7)	1.31 (1.10, 1.56)	0.644	2.05 (1.76, 2.39)	0.913	0.43 (0.36, 0.51)	0.062
Hearing loss (>15 dB) at high frequency[b]							
No	758 (87.3)	1.25 (1.21, 1.30)		2.05 (1.97, 2.15)		0.36 (0.34, 0.38)	
Yes	95 (12.7)	1.32 (1.19, 1.46)	0.336	1.91 (1.70, 2.14)	0.263	0.41 (0.37, 0.45)	0.023
Sex							
Male	433 (53.1)	1.42 (1.36, 1.48)		2.11 (2.00, 2.22)		0.37 (0.34, 0.40)	
Female	420 (46.9)	1.10 (1.04, 1.17)	<0.001	1.96 (1.86, 2.06)	0.036	0.35 (0.33, 0.38)	0.339
Household income							
Low	217 (29.7)	1.26 (1.19, 1.33)		2.02 (1.87, 2.18)		0.40 (0.36, 0.44)	
Low-middle	200 (25.1)	1.33 (1.25, 1.42)		2.02 (1.88, 2.17)		0.37 (0.34, 0.41)	
High-middle	215 (23.8)	1.21 (1.09, 1.34)		2.03 (1.87, 2.19)		0.33 (0.30, 0.36)	
High	221 (21.5)	1.24 (1.17, 1.31)	0.334	2.08 (1.90, 2.28)	0.648	0.34 (0.31, 0.37)	0.013
Education							
≤Elementary school	431 (44.3)	1.28 (1.23, 1.33)		2.09 (1.98, 2.20)		0.37 (0.35, 0.39)	
Middle school	302 (38.2)	1.19 (1.12, 1.27)		1.92 (1.81, 2.04)		0.34 (0.31, 0.37)	
High school	119 (17.4)	1.37 (1.22, 1.53)		2.15 (1.97, 2.36)		0.38 (0.33, 0.43)	
≥College	1 (0.1)	1.84 (1.84, 1.84)	0.573	1.64 (1.64, 1.64)	0.878	0.37 (0.37, 0.37)	0.770
Body mass index (kg/m^2)							
<25	750 (87.0)	1.25 (1.21, 1.29)		1.99 (1.92, 2.08)		0.36 (0.34, 0.38)	
≥25	103 (13.0)	1.37 (1.20, 1.57)	0.161	2.33 (2.10, 2.57)	0.004	0.37 (0.32, 0.42)	0.830
Cigarette smoking							
Never smoker	781 (89.6)	1.24 (1.20, 1.28)		2.01 (1.93, 2.10)		0.35 (0.33, 0.36)	
Current smoker	72 (10.4)	1.46 (1.33, 1.60)	0.001	2.22 (1.97, 2.50)	0.114	0.54 (0.44, 0.66)	<0.001
Recreational noise exposure							
No	531 (60.0)	1.26 (1.21, 1.32)		2.06 (1.96, 2.17)		0.36 (0.34, 0.38)	
Yes	322 (40.0)	1.26 (1.19, 1.34)	0.965	1.99 (1.88, 2.11)	0.353	0.37 (0.34, 0.39)	0.743
Firearm noise exposure							
No	832 (98.1)	1.26 (1.22, 1.30)		2.04 (1.96, 2.12)		0.36 (0.34, 0.38)	
Yes	21 (1.9)	1.45 (1.22, 1.72)	0.111	1.87 (1.60, 2.19)	0.299	0.40 (0.27, 0.58)	0.612

Note: *p*-Value based on survey t-test for binominal groups and based on Wald test for categorical groups. Weighted percentages based on survey frequency.
[a]Pure tone average at 0.5, 1, 2, and 4 kHz.
[b]Pure tone average at 3, 4, and 6 kHz.

frequency hearing loss compared with the lowest quartiles of blood cadmium and blood lead, respectively. These associations remained statistically significant when both metals were included in the model. Our observations from adults were consistent with the results of previous epidemiological studies. In a recent study of 3,698 adults 20–69 y old using the U.S. NHANES, subjects in the highest quintile of blood cadmium (0.8 – 8.5 μg/L) compared with those in the lowest quintile (<0.2 μg/L) had an OR of 1.74 (95% CI: 1.12, 2.70) for speech-frequency hearing loss with a significant linear trend (Choi et al. 2012a). In addition, a longitudinal study of 448 older men found that an interquartile range increase in patella bone lead levels was associated with an OR of 1.48 (95% CI: 1.14, 1.91) for speech-frequency hearing loss (Park et al. 2010).

We found a greater association between blood cadmium and hearing loss in adolescents (OR = 3.03 for high-frequency hearing loss in the highest quartile vs. lowest) than that in adults (OR = 1.47). The association between blood lead and high-frequency hearing loss in adolescents was comparable to that found in adults but did not reach statistical significance, most likely because of the small sample size and thus the low power. These findings are in accord with those of a previous study of U.S. NHANES adolescents: individuals in the highest quartile of urinary cadmium [median: 0.15 μg/g creatinine (vs. lowest)] had an OR of 3.08 (95% CI: 1.02, 9.25) for low-frequency hearing loss (average of thresholds at 0.5, 1, and 2 kHz >15 dB), but the highest quartile of blood lead (median: 1.59 μg/dL) was not associated with hearing loss (Shargorodsky et al. 2011). That study, however, found that highly exposed subjects (5.4%) with blood lead >2 μg/dL (vs. <1 μg/dL) had an OR of 2.22 (95% CI: 1.39, 3.56) for high-frequency hearing loss (average of thresholds at 3, 4, 6, 8 kHz >15 dB, $n = 2{,}535$). In the present study, we also found a stronger association between blood lead and hearing loss when using the same cut-off point for blood lead (>2 μg/ dL vs. <1 μg/dL; data not shown), but that association did not reach statistical significance most likely because of the different definition of high frequency (not available for 8 kHz) and the smaller sample size ($n = 853$).

Lead and cadmium share common pathways leading to ototoxicity, including oxidative stress through depletion of the thiol pool and inhibition of antioxidant defense systems (Park 2015). Experimental studies of lead exposure have suggested that lead-induced oxidative stress in mitochondria and reduced blood flow in the cochlea result in degeneration of inner ear receptor cells (Lasky et al. 1995; Yamamura et al. 1989). Lead can also disturb the auditory brainstem (Jones et al. 2008). Experimental studies of cadmium exposure have suggested that cadmium-induced oxidative stress causes apoptosis and alters the arrangement of inner ear receptor cells, leading to an elevation in auditory thresholds (Kim et al. 2008; Ozcaglar et al. 2001).

Our results support existing evidence that the low-level exposures to lead and cadmium currently observed in the general population of adults and adolescents may influence the risk of hearing loss. The U.S. CDC's Advisory Committee for Childhood Lead Poisoning Prevention recommended 5 μg/dL as the reference value for children (CDC 2014); in our population, only one adolescent had a blood lead level >5 μg/dL. Although there is no reference for general adults, the U.S. OSHA safety standards are currently 38.6 μg/dL (1.93 μmol/L) for lead and 5 μg/L (44.5 nmol/L) for

Table 3. Odds ratios (ORs) [95% confidence intervals (CIs)] of hearing loss (>25 dB) by blood lead, mercury, and cadmium levels in single-pollutant models in adults ($n = 5,187$).

Variables[a]	Speech-frequency PTA[b]		High-frequency PTA[c]	
	No. hearing loss/No. participants	ORs (95% CIs)	No. hearing loss/No. participants	ORs (95% CIs)
Lead				
Per doubling of lead	1,124/5,187	1.15 (0.94, 1.41)	1,124/5,187	1.30 (1.08, 1.57)
Lead quartile (μg/dL)				
Q 1 (0.327–1.593)	170/1,296	1 (Reference)	276/1,296	1 (Reference)
Q 2 (1.594–2.146)	204/1,296	0.94 (0.65, 1.35)	420/1,296	1.13 (0.83, 1.53)
Q 3 (2.148–2.822)	330/1,298	1.29 (0.92, 1.78)	587/1,298	1.35 (1.00, 1.81)
Q 4 (2.823–26.507)	420/1,297	1.25 (0.87, 1.79)	810/1,297	1.70 (1.25, 2.31)
p-Trend		0.066		<0.001
Mercury				
Per doubling of mercury	1,124/5,187	0.96 (0.84, 1.08)	1,124/5,187	0.98 (0.87, 1.09)
Mercury quartile (μg/L)				
Q 1 (0.363–2.378)	284/1,296	1 (Reference)	469/1,296	1 (Reference)
Q 2 (2.379–3.528)	250/1,297	0.84 (0.61, 1.17)	460/1,297	0.89 (0.68, 1.16)
Q 3 (3.529–5.369)	267/1,296	0.79 (0.58, 1.09)	524/1,296	0.83 (0.63, 1.08)
Q 4 (5.370–60.678)	323/1,298	0.84 (0.63, 1.12)	640/1,298	0.89 (0.68, 1.17)
p-Trend		0.221		0.382
Cadmium				
Per doubling of cadmium	1,124/5,187	1.18 (1.00, 1.39)	1,124/5,187	1.25 (1.08, 1.44)
Cadmium quartile (μg/L)				
Q 1 (0.068–0.689)	140/1,293	1 (Reference)	289/1,293	1 (Reference)
Q 2 (0.690–1.033)	255/1,300	1.04 (0.73, 1.49)	489/1,300	1.10 (0.81, 1.49)
Q 3 (1.035–1.470)	340/1,299	1.22 (0.86, 1.72)	645/1,299	1.43 (1.06, 1.93)
Q 4 (1.471–6.422)	389/1,295	1.30 (0.88, 1.91)	670/1,295	1.47 (1.05, 2.05)
p-Trend		0.117		0.007

Note: Models were adjusted for age, age^2, sex, education, body mass index, cigarette smoke, current diagnosis of hypertension, current diagnosis of diabetes, occupational noise, recreational noise, and firearm noise. PTA, pure tone average.
[a]Hearing loss was defined as pure tone average >25dB.
[b]Speech-frequency PTA at 0.5, 1, 2, and 4 kHz.
[c]High-frequency PTA at 3, 4, and 6 kHz.

cadmium in whole blood [Agency for Toxic Substances and Disease Registry (ATSDR) 2010a,b]; the Korea OSHA reference for occupational disease diagnosis are 40 μg/dL for lead and 5 μg/L for cadmium (KOSHA 2016). In our population, no adult exceeded that limit for lead and very few adults (0.1%) exceeded that limit for cadmium. Our findings, therefore, provide evidence that low levels of lead and cadmium exposure, even below the levels in the U.S. CDC guidance and the U.S. and Korea OSHA regulations, can influence hearing loss. Although the major historical sources of lead exposure such as gasoline, paint, and solder have decreased considerably in many countries, the use of lead continues to be widespread, and its accumulation in the human body can influence the development of chronic diseases (Hu et al. 2006; Muntner et al. 2005). The major sources of cadmium exposure are cigarette smoke, ambient air pollution, and dietary intake of contaminated vegetables, grain, and shellfish (Järup et al. 1998), and a major source particularly in Korea includes high consumption of rice (Park and Lee 2013b). There is growing evidence that current environmental levels of lead and cadmium have adverse effects on various health outcomes including renal function, hypertension, and macular degeneration (Hu et al. 1996; Navas-Acien et al. 2009; Tellez-Plaza et al. 2007; Wu et al. 2014) in addition to our findings for hearing loss; therefore, efforts to reduce environmental exposure to lead and cadmium are needed to improve public health.

The present study did not find evidence that blood mercury is associated with an increased risk of hearing loss among adults or adolescents. This finding is consistent with the results of previous studies of U.S. adolescents and Andean adults (Counter et al. 1998; Counter et al. 2012; Shargorodsky et al. 2011). An epidemiologic study of general U.S. adolescents failed to observe significant associations between blood mercury and hearing loss (Shargorodsky et al. 2011), explaining that environmental levels of exposure to mercury in U.S. adolescents (median levels of 0.39–0.63 μg/L blood mercury) may not have a detectable power to observe a significant association with hearing loss. In studies conducted in Andean gold-mining areas, no significant associations between blood mercury (median level of 6 μg/L) and hearing thresholds were found in adults (sample size ranged from 29 to 39) (Counter et al. 1998, 2012), yet a statistically significant association was found between blood mercury (median levels of 7–23 μg/L) and hearing thresholds in children. In the general population, the use of mercury is widespread: metallic and inorganic mercury exposure occur mainly through dental amalgams and occupational exposure (gold mining and industrial settings), and exposure to methylmercury (known to be more common and more toxic) occurs through dietary intake of fish and shellfish (ATSDR 1999). The present study used blood mercury as an exposure biomarker that captures both inorganic mercury and methylmercury (ATSDR 1999). The levels of blood mercury in our KNHANES population (medians of 3.53 μg/L for adults and 1.96 μg/L for adolescents) are relatively higher than those found in other countries owing to higher consumption of fish and shellfish (Park and Lee 2013b) and rice (Lee et al. 2006). However, additional adjustment for fish consumption did not change the results (Table S7). It is unclear whether confounding by fish consumption did not exist in this study or fish consumption from the FFQ did not capture actual omega-3 fatty acid consumption because of measurement error. Given mercury's neurotoxicity, including toward the auditory nervous system (Murata et al. 1999), future studies with different types of biomarkers—such as urine (an indicator of elemental mercury) and hair (an indicator of methylmercury) along with a good measure of fish consumption and omega-3 fatty acids—are warranted to confirm our findings.

The strengths and limitations of this study should be considered. This study used data from a large representative sample of the Korean general population and was adjusted for important potential confounders, including recreational noise (i.e., loud noise outside of work, earphone music in noisy places), occupational noise, firearm noise, and clinically important risk factors

Table 4. Odds ratios (ORs) [95% confidence intervals (CIs)] of hearing loss (>15 dB) by blood lead, mercury, and cadmium levels in single-pollutant models in adolescents ($n = 853$).

Variables[a]	Speech-frequency PTA[b]		High-frequency PTA[c]	
	No. hearing loss/No. participants	ORs (95% CIs)	No. hearing loss/No. participants	ORs (95% CIs)
Lead				
Per doubling of lead	48/853	1.20 (0.48, 3.05)	95/853	1.26 (0.73, 2.16)
Lead quartile (μg/dL)				
Q 1 (0.260–0.975)	11/213	1 (Reference)	20/213	1 (Reference)
Q 2 (0.978–1.260)	12/213	1.17 (0.41, 3.32)	20/213	0.89 (0.39, 2.03)
Q 3 (1.261–1.557)	13/213	1.08 (0.38, 3.08)	31/213	1.88 (0.83, 4.25)
Q 4 (1.562–5.904)	12/214	1.24 (0.34, 4.49)	24/214	1.38 (0.63, 3.02)
p-Trend		0.803		0.181
Mercury				
Per doubling of mercury	48/853	1.01 (0.53, 1.91)	95/853	0.73 (0.45, 1.20)
Mercury quartile (μg/L)				
Q 1 (0.555–1.488)	13/213	1 (Reference)	32/213	1 (Reference)
Q 2 (1.490–1.956)	10/213	1.00 (0.36, 2.75)	20/213	0.64 (0.30, 1.36)
Q 3 (1.960–2.683)	11/214	0.60 (0.21, 1.75)	17/214	0.34 (0.16, 0.74)
Q 4 (2.687–8.409)	14/213	1.20 (0.41, 3.54)	26/213	0.58 (0.27, 1.26)
p-Trend		0.901		0.107
Cadmium				
Per doubling of cadmium	48/853	1.41 (0.93, 2.14)	95/853	1.54 (1.12, 2.11)
Cadmium quartile (μg/L)				
Q 1 (0.010–0.245)	12/214	1 (Reference)	20/214	1 (Reference)
Q 2 (0.246–0.341)	9/213	0.96 (0.33, 2.76)	17/213	1.06 (0.46, 2.46)
Q 3 (0.342–0.495)	9/213	0.93 (0.33, 2.66)	20/213	1.51 (0.68, 3.37)
Q 4 (0.496–2.067)	18/213	2.39 (0.98, 5.83)	38/213	3.03 (1.44, 6.40)
p-Trend		0.083		0.003

Note: Models were adjusted for age, age^2, sex, education, body mass index, cigarette smoke, recreational noise, and firearm noise. PTA, pure tone average.
[a]Hearing loss was defined as PTA > 15dB.
[b]Speech-frequency PTA at 0.5, 1, 2, and 4 kHz.
[c]High-frequency PTA at 3, 4, and 6 kHz.

(i.e., diabetes, hypertension). Moreover, the present study was conducted in two different subsets of adults and adolescents, allowing us to better understand different susceptibilities in the association between heavy metals and hearing loss. However, several limitations should be considered. First, our study is cross-sectional, so we cannot make an inference about the temporal causation of exposures and hearing loss; there is a potential for reverse causality. Second, lead and mercury concentrations in blood mainly reflect recent exposures. Blood lead has a short half-life (i.e., ~30 d), enabling a measure of current lead exposure, whereas bone lead, with its long-term accumulation, enables a measure of chronic exposure (Hu et al. 1998). Indeed, a previous study using bone lead measurements supports its chronic effect on aging-related hearing loss (Park et al. 2010). Third, we cannot rule out potential exposure misclassification and residual confounding by noisy environments that were not captured by the dichotomous variables of occupational noise, recreational noise, and firearm noise. Fourth, no data were available for congenital cytomegalovirus infection or for genetic defects. Subjects were therefore not excluded on the basis of either condition, nor was either condition controlled for as a covariate. Fifth, secondhand smoke may be a potential confounder in adolescents, but we did not adjust for it owing to a lack of data in KNHANES adolescents. Sixth, important potential confounders such as occupational noise and clinical diseases were adjusted for in adults but were not adjusted for in adolescents because of a lack of data. Given the low prevalence of occupational noise and clinical diseases in adolescent populations, their impacts would be minimal. Finally, the low prevalence of hearing loss in adolescents resulted in wider confidence intervals for the ORs; therefore, actual associations may be more significant than our observations.

Conclusions

In summary, the present analysis of a well-defined representative sample of Korean adults found a significant association between current exposures to environmental lead and cadmium in the general Korean population and the risk of hearing loss independent of known risk factors including various noise exposures and clinical risk factors. Cadmium exposure also seems to increase the risk of hearing loss in adolescents. However, we found no significant association between environmental mercury exposure and hearing loss in either adults or adolescents. Our findings have significant public health implications; efforts to reduce environmental exposures to lead and cadmium are important to prevent hearing loss in the general population. Further studies with prospective designs and wide ranges of exposure are needed to confirm concerns related to causal inferences and problems of reverse causality of the association.

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