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Environmental Cadmium Exposure, Chronic Suppurative Otitis Media, and Hearing Impairment

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Abstract

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Chronic suppurative otitis media (CSOM) and hearing impairment are associated with oxidative stress, which could be induced by cadmium exposure. Few studies have investigated the association among cadmium, CSOM, and hearing impairment. We evaluated the role of CSOM as a mediator in the association between environmental cadmium exposure and hearing impairment among adults.

This cross-sectional study evaluated 5,838 adults aged 20–69 years who were enrolled in the Korean National Health and Nutrition Examination Survey from 2009 to 2012 and had cadmium measurements. CSOM was diagnosed by otologic examination and hearing impairment was defined as a

pure-tone average (PTA) of 0.5, 1, 2, and 4 kHz >25 dB in the better ear. Results: Weighted prevalence was 2.9% for CSOM and 7.7% for hearing impairment. After adjusting for age, sex, smoking status, and body mass index, the odds ratio for CSOM by environmental cadmium exposure was 3.91 (95% confidence interval: 1.72, 8.86) and that for hearing impairment was 1.66 (95% confidence interval: 1.02, 2.71), comparing the highest vs. lowest quartile of blood cadmium levels. The association between blood concentration of cadmium and hearing impairment measured by PTA in both ears was found to be mediated by CSOM (Sobel = 5.564, $p < 0.001$) at a mediation percentage of 5%.

We found that environmental cadmium exposure is associated with CSOM and hearing impairment in the adult population. In addition to the independent relation between cadmium exposure and hearing impairment, CSOM plays a mediating role partly in the association between exposure to cadmium and hearing impairment.

keywords: cadmium; otitis media, suppurative; hearing loss
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Contents

Introduction

Cadmium is a toxic heavy metal used for various industrial purposes. It has been used as an anti-corrosive, stabilizing, or coloring agent in such processes and products as electroplating, plastics, pigmentation for rubber or inks, alloy production, nickel-cadmium batteries, photoelectric cells, and semiconductors. Cadmium production, consumption, and emissions into the environment have increased dramatically in the 20th century [1]. Cadmium exposure occurs primarily through dietary intake from food and drinking water, tobacco smoke, and occupational exposure [2]. It has been shown in previous studies that cadmium exposure can lead to osteoporosis, renal dysfunction, diabetes, cancer, high blood pressure, and reproductive problems [3].

Hearing impairment was the second leading cause of long-term disability in the world, following depression [4]. Recently, hearing impairment has been considered as one of the health effects of environmental cadmium exposure. A study using the data from the National Health and Nutrition Examination Survey (NHANES) reported that urinary cadmium levels were positively associated with hearing impairment in U.S. adolescents [5]. Another study using data from NHANES, 1999–2004, identified cadmium exposure as an important risk factor for hearing impairment in the U.S. adult population [6]. Chronic suppurative otitis media (CSOM), one of the most common otologic diseases, affects 65–300 million people worldwide, and accounts for much of the considerable burden of hearing impairment. Chronic otitis media is clinically characterized by persistent inflammation of the middle ear, which describes all types of otitis media that fail to resolve after an acute episode. CSOM, a type of the chronic otitis media, is defined by the World Health

Organization as a chronic inflammation of the middle ear and mastoid cavity, which presents with recurrent ear discharges or otorrhea through a tympanic perforation [7].

Recently, some researchers suggested that imbalance between oxidative stress and antioxidant enzymes has a significant role in development of CSOM [8,9]. Oxidative stress in cadmium toxicity has been well established as playing a central role in various cadmium-induced pathologies [10]. Oxidative stress has also been suggested as a possible mechanism of hearing impairment by inducing apoptosis and reactive oxygen species generation [11,12]. The results of these studies indicate that CSOM and hearing impairment may share oxidative stress as a contributing factor caused by cadmium. However, the association between cadmium, CSOM, and hearing impairment has yet to be clarified.

The specific aims of our study were to investigate the following: (1) evaluation of the association between blood cadmium level, CSOM, and hearing impairment; and (2) exploration of the potential mediating effect of CSOM in the association between blood cadmium level and hearing impairment.

Materials and methods

Study design and participants

Data were derived from the Korean National Health and Nutrition Examination Survey (KNHANES) 2009–2012, which was a cross-sectional, nationally representative survey conducted by the Korean Centers for Disease Control and Prevention. The survey was conducted using a rolling sampling design that involves a complex, stratified, multistage, probability-cluster evaluation of a representative sample of the non-institutionalized civilian population in Korea. The KNHANES data set is publicly available. The Institutional Review Board of the Korean Centers for Disease Control and Prevention approved this survey, and all participants provided written informed consent for participation in the study.

In 2009, 2,000 participants, aged ≥20 years, were randomly and proportionally selected for measurement of blood concentration of cadmium. Annually, 2,400 participants were selected for measurement of blood cadmium level from 2010 to 2012. Of 36,067 total participants, therefore, blood cadmium data are available for 9,153. Participants under 20 years of age or above 69 years of age (n = 1,553); those with missing information on otologic examination and audiometric examination (n = 1,696); and those with missing information on sex, age, weight, height, and smoking status (n = 66) were excluded. The final sample size used in this analysis was 5,838 (figure 1).

Variables

Height and weight were measured during the examination procedure. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was classified into two groups: <25 kg/m^2 and ≥25 kg/m^2. Smoking status was categorized as never-, former-, and current-smoker. Blood cadmium level was measured at the Neodin Medical Institute, which was certified by the Korean Ministry and Health and Welfare. Graphite furnace atomic absorption spectrometry was used to measure cadmium concentration by using the PerkinElmer AAnalyst (PerkinElmer Wallac Oy, Turku, Finland) with dibasic ammonium phosphate Triton X-100 (Sigma-Aldrich, St. Louis, MO) and concentrated nitric acid (Dongwoo Fine-Chem, Pyeongtaek, Korea).

Otological and Audiometric examination

The presence of CSOM was examined by otolaryngologists. CSOM was diagnosed when the subject had tympanic membrane perforation and/or cholesteatoma, excluding congenital cholesteatoma after examination using a 4-mm 0°-angled rigid endoscope. Patients with deep retraction pockets and keratin or otorrhea were diagnosed with cholesteatoma, including attic, sinus, and tensa retraction cholesteatoma. Patients with otitis media with effusion, severe cerumen plug, otorrhea too severe to allow examination of the tympanic membrane, post-operative state, or stenosis in the external auditory canal were excluded.

Audiometry examinations were conducted in a sound-isolated room with an

automatic digital diagnostic audiometer (Model SA203; Entomed Diagnostics AB, Lena Nodin, Sweden). According to the grades of hearing impairment classified by the World Health Organization, a pure-tone average (PTA) at 0.5, 1, 2, and 4 kHz greater than 25 dB in the better ear was defined as hearing impairment [13,14].

Statistical analysis

Since the blood concentration of cadmium was not normally distributed, we used log-transformed values for analysis. Geometric mean (GM) values and 95% confidence intervals (CIs) of blood cadmium were calculated according to CSOM status, sex, age group, smoking status, and BMI group.

Multiple logistic regression analysis was performed to examine the association between concentrations of blood cadmium and CSOM prevalence or hearing impairment. Odds ratios (ORs) were estimated by comparing each quartile to the lowest quartile of cadmium blood concentration. We ran an unadjusted model and two other models with progressive adjustment for possible confounding factors. Model 1 was adjusted for age (grouped as 25–39, 40–54, and 55–69 years) and sex. Model 2 further included BMI (<25 and ≥25 kg/m^2) and smoking status (never smoker, former smoker, current smoker).

Considering the complex survey design, t-test was performed to compare the differences in PTA between normal and CSOM patients. Participants were categorized into four groups by CSOM status in each ear: Group 1 (normal), Group 2 (affected in the right ear only), Group 3 (affected in the left ear only), and Group 4 (both ears affected).

Mediation analysis was performed to determine the association between concentration of blood cadmium level and hearing threshold, with CSOM status as the mediator (figure 2). This method involves estimation of three regression equations.

Equation 1: $Y = b_{01} + cX$

Equation 2: $M = b_{02} + aX$

Equation 3: $Y = b_{03} + c'X + bM$

In this analysis, coefficient c in Equation 1 was considered as the direct effect of the causal variable X (blood cadmium level) on the outcome variable Y (mean value of PTA in both ears), without effect of mediator M (CSOM). Next, coefficient b relating M to Y (Equation 1) and the coefficient a relating X to M (Equation 2) were computed. Coefficient c' is the effect of X on Y controlling for M. The product of these two parameters ab is the indirect effect, and equivalent to $c - c'$. The Sobel test has been developed to evaluate the null hypothesis that $ab = 0$. In this analysis, blood cadmium concentration and hearing threshold were continuous variables, while CSOM status was a dichotomous variable. We used the statistical solution for mediation analysis with a dichotomous mediator presented by MacKinnon and Dwyer [15] and used the SAS macro for mediation analysis developed by Jasti et al. [16].

We performed several sensitivity analyses. First, data were analyzed after excluding participants with extreme blood cadmium levels (more than 2 standard deviations from the GM). Second, we included only non-smokers in the analyses to exclude the residual effects of smoking. Third, we excluded participants aged 65 years or older in the analysis because age-related hearing loss (presbycusis) could be overlapped with the sensorineural hearing loss

affected by cadmium exposure. Finally, we investigated that the association between blood cadmium level and hearing impairment within participants with CSOM status.

Statistical analysis was performed using SAS SURVEYMEANS, SAS SURVEYFREQ, SAS SURVEYREG, and SAS SURVEYLOGISTIC procedures (Version 9.3; SAS Institute Inc., Cary, NC) to account for the complex survey design and sample weights. We computed 4-year sample weights, as recommended by Korean Centers for Disease Control and Prevention. Statistical significance was defined as two-sided $p \leq 0.05$.

Results

Of the total 5,838 participants, 2,854 were male and 2,984 were female, and the mean age was 41.93 and 42.70 years, respectively (table 1). One hundred and sixty-four participants were diagnosed with CSOM, and the weighted prevalence was 2.9%. Five hundred and forty-six participants had hearing impairment, and the weighted prevalence was 7.7%. Older ages and hearing impairment were associated with CSOM. In our study population, GM of blood cadmium was 0.91 μg/L. CSOM status, female sex, older age, higher BMI, current smoking, and hearing impairment were significantly associated with higher levels of blood cadmium.

There was a positive association between blood concentration of cadmium and CSOM prevalence. Using multiple logistic regression models, ORs and 95% CIs for each quartile of blood cadmium compared with the lowest quartile as the referent were calculated in three different models as described above (table 2). ORs for the highest quartile compared to the lowest quartile in the unadjusted model, model 1, and model 2 were 5.74 (95% CI 2.88 to 11.44), 3.08 (95% CI 1.40 to 6.77), and 3.91 (95% CI 1.72 to 8.86), respectively. Trend tests were also statistically significant in all models. Higher blood cadmium levels were positively associated with hearing impairment in the unadjusted and adjusted models (table 3). ORs for hearing impairment in the highest blood cadmium quartile compared to the lowest quartile in the unadjusted model, model 1, and model 2 were 3.86 (95% CI 2.59 to 5.75), 1.76 (95% CI 1.11 to 2.79), and 1.66 (95% CI 1.02 to 2.71, respectively. Trend test was statistically significant in the unadjusted model and model 1, and marginally statistically significant in model 2.

We found differences in PTA and proportion of hearing impairment by CSOM status (table 4). Compared to the unaffected group, the right-ear-only affected group and both-ears affected group showed a higher PTA in the right side, and these differences were statistically significant (13.35 dB, 36.45 dB, 27.33 dB, respectively). The results were similar for the left side. As compared to the unaffected group, left-ear-only affected group, and both-ears affected group showed a higher PTA in the left side (13.18 dB, 32.83 dB, 32.49 dB, respectively). In the mediation analysis, CSOM status mediated the association between blood concentration of cadmium and PTA, and the percent mediated was 5.00% (Sobel = 5.564, $p < 0.001$) (table 5)

We performed sensitivity analysis and the results were insensitive to extreme values of blood cadmium (tables 6-9). The results calculated after exclusion of former- and current-smoking participants (table 10-13) and the results calculated after excluding participants aged 65 years or older were also robust (tables 14-17). Associations between blood cadmium and CSOM, between blood cadmium and hearing impairment, and between CSOM and hearing impairment were concordant with the findings for the full data set. However, the association between blood cadmium concentration and hearing impairment was not statistically significant within participants with CSOM (tables 18-19).

Discussion

In a representative sample of Korean adults who enrolled in KNHANES, 2009–2012, we found that environmental cadmium exposure was associated with CSOM and hearing impairment. The association between cadmium exposure and hearing impairment was partially mediated by CSOM.

As urinary cadmium levels were not measured in KNHANES 2009-2012, we used blood concentration of cadmium as a marker of environmental exposure to cadmium. Although urinary cadmium levels were known to reflect body burden well, blood cadmium is also associated with the body burden of cadmium in general population [1]. Furthermore, it was established that urinary cadmium levels was mainly correlated with blood cadmium levels [17].

The main source of cadmium exposure for general population is known to be consumption via food. Cadmium from industrial or agricultural sources could contaminate soils and increase cadmium uptake in crops and vegetables that are grown for human consumption [18]. In general, leafy vegetables such as lettuce, spinach, potatoes, grains, legumes, and sunflower seeds contain more cadmium than other foods [19]. Cadmium absorption through the respiratory system, such as through smoking, is another important possible source of exposure. It is estimated that smoking 20 cigarettes per day is as same as absorbing about 1 μg of cadmium [1]. Environmental tobacco smoke could also be a source of cadmium exposure through inhalation[20]. Therefore, cadmium exposure due to cigarette smoking was considered as a confounder or mediator in our analysis. On the other hand, although house dust could be an important route of exposure to cadmium in areas with contaminated soil, it

is known that cadmium in ambient air contributes only to a small percentage of the burden of cadmium in the body [21,22]. The cadmium concentrations in ambient air were not available in this study.

In the present analysis, GM of blood cadmium of Koreans aged 20 to 69 was 0.91 μg/L (95% CI: 0.87, 0.95), and GM of blood cadmium level was lower in men than in women (0.75 μg/L vs. 1.10 μg/L, respectively). Higher levels of cadmium in women than men may be related with the higher occurrence of iron deficiency in women due to menstruation and pregnancy. It has been shown that intestinal absorption of dietary cadmium is increased during periods of iron deficiency [23,24]. In the Korean population, the GM of blood cadmium was higher than in Canadian and U.S. populations. In a national representative survey in Canada, the GM of blood cadmium level in adults aged 20–79 years was 0.42 μg/L [25]. In the study using National Health and Nutrition Examination Survey Data, 1999–2004, in the U.S., the GM of blood cadmium level was also 0.42 μg/L [26]. A possible explanation for the difference in blood cadmium level is that Korean people are exposed to high levels of cadmium through the intake of foods with high cadmium levels, such as rice [27]. However, the reason Korean people show higher cadmium levels is yet to be clarified. There is also a study showing that dietary exposure to cadmium in the Korean population is comparable to those reported from the U.S. (14.3 μg Cd/person versus 15 μg Cd/person) [28].

The health effects of cadmium have been shown to include renal failure, bone fragility, reproductive outcomes, renal cell cancer, breast cancer, prostate cancer, and colorectal cancer [29]. In addition to these health effects, it was reported that otitis media is related with environmental cadmium exposure such as air pollution or environmental tobacco smoke[30]. However, there have been very few studies evaluating the association between cadmium

exposure and CSOM. Recently, it was investigated that COM was associated with increased levels of cadmium[31].

According to several studies, Eustachian tube dysfunction and recurrent middle ear cavity infection was associated with the pathogenesis of CSOM [32]; cadmium exposure could potentially alter immune system and mucociliary function of the upper airway [33,34]; and reduced ciliary function has been associated with clearance of middle-ear secretions and progression of CSOM [35,36].

There have also been studies about the effects of cadmium on the auditory system. It has been shown that Cochlear inner hair cells, which transduce mechanical auditory stimuli into electrical impulse, are as sensitive to cadmium as kidney tubule cells because of the functional resemblance between them [37]. In an experimental animal study, hair cells in the auditory system were found to be more sensitive to cadmium than kidney tubule cells [38]. In other experimental studies conducted with the auditory HEI-OC1 cell line, cadmium exposure caused reactive oxygen species generation and cell death, and an antioxidant was found to have a protective effect [11]. Recently, epidemiologic evidence has suggested that even the low-level exposure to cadmium currently observed in the U.S. general population could be associated with hearing loss [6].

It is well known that CSOM is a cause of hearing impairment, mainly conductive and partially sensorineural hearing loss [39-41]. More than 50% of patients with CSOM develop mild to moderate hearing loss [41]. Hearing impairment may be caused by disruption of eardrum and ossicles assembly and hair cell damage by a bacterial infection that has penetrated the inner ear [42].

In our investigation of the effect of cadmium on CSOM, hearing impairment,

and mediation of the effect, we found that higher blood cadmium levels were associated with higher prevalence of CSOM and hearing impairment. Moreover, the mediation analysis showed the percent effect of mediation was 5%, which was statistically significant. In prior studies on the association between cadmium and hearing impairment, cadmium was believed to induce hearing impairment through its effect on the inner hair cells and result in sensorineural hearing loss. Our study suggests that CSOM is another pathway by which cadmium can induce hearing impairment.

Sensitivity analysis was conducted in participants with blood cadmium ranging within GM±2 SD to ensure that our findings were not influenced by extreme values. In addition, sensitivity analyses to rule out the effect of smoking, a possible confounding factor, and the effect of presbycusis were also conducted. In these analyses, we observed the findings were robust. There was not statistically significant association between blood cadmium level and hearing impairment only within subjects with CSOM. However, the result may be affected by small number of subjects with CSOM or by relatively much smaller effect of blood cadmium level than effect of disease status of participant on hearing loss.

We used data from a representative sample of the Korean population to reduce sampling bias. By integrating results from surveys taken over 4 years, a considerable number of participants was included in our study. In addition, accurate measurements of cadmium concentration in blood, qualified audiometry test, and examinations for CSOM status by an otolaryngologist support the internal validity of our study. Furthermore, the effect of cadmium on CSOM and hearing impairment might be observed more clearly in this study population than in other populations whose blood cadmium levels was lower.

Despite these strengths, our study has some limitations. Our study used a cross-sectional design, which makes it difficult to conclude a causal relationship among cadmium exposure, CSOM, and hearing impairment. Although there is a possibility of reverse causality in a cross-sectional study design, however, it would be illogical to consider hearing impairment as the cause of cadmium exposure. In addition, the results of our study have limited applicability to populations of other countries and ethnicities, as the KNHANES data included only Korean participants. Furthermore, occupational exposure to cadmium was not considered in our study because the KNHANES survey did not include an occupation/job code precisely enough to allow us to screen for jobs involving cadmium exposure.

Conclusion

In conclusion, our study supports the hypothesis that environmental cadmium exposure is associated with CSOM and hearing impairment, and that CSOM mediates the effect of cadmium exposure on hearing impairment partially. The results of this study revealed another health effect of environmental cadmium exposure, and as such, more efforts in reducing sources of cadmium exposure are necessary for improving public health, particularly given the high prevalence of hearing impairment.

Figure 1. Schematic diagram depicting study population

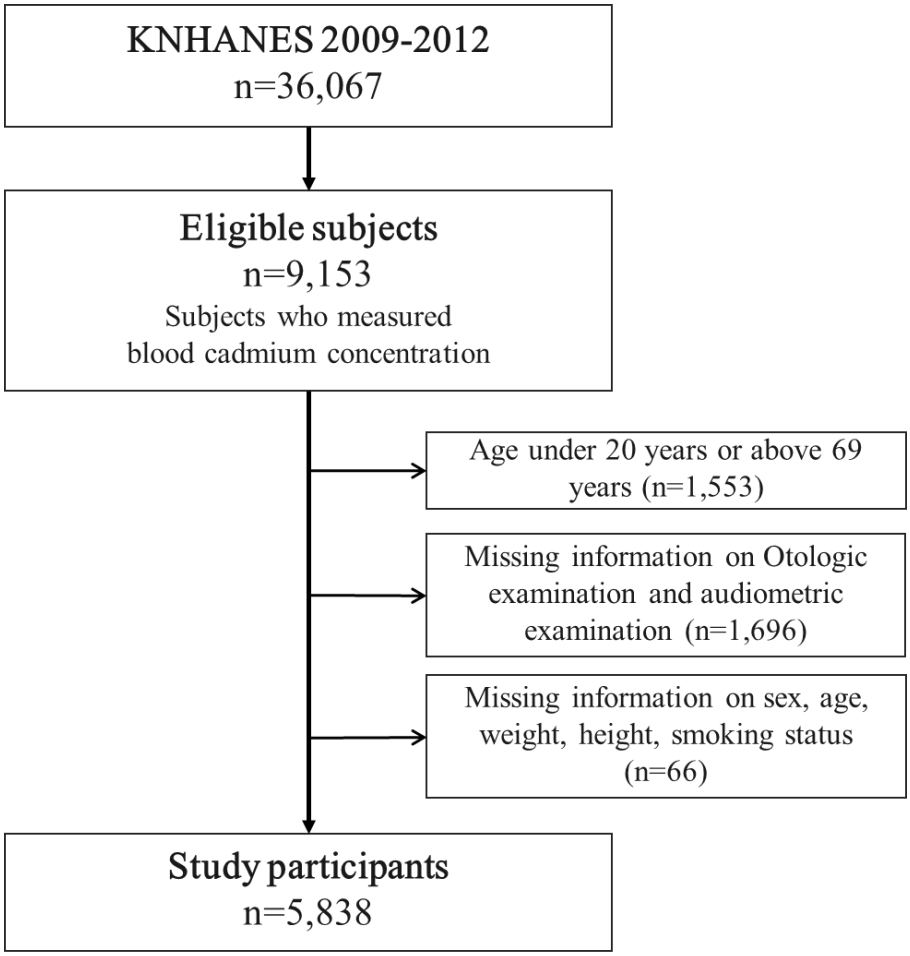

Figure 2. Model for mediation analysis

Causal variable X = log transformed blood concentration of cadmium. Mediator variable M = chronic suppurative otitis media (CSOM). Outcome variable Y = mean value of pure tone average (PTA) in both ears. Direct effect = c'; mediated effect = ab; total effect = c' + ab = c

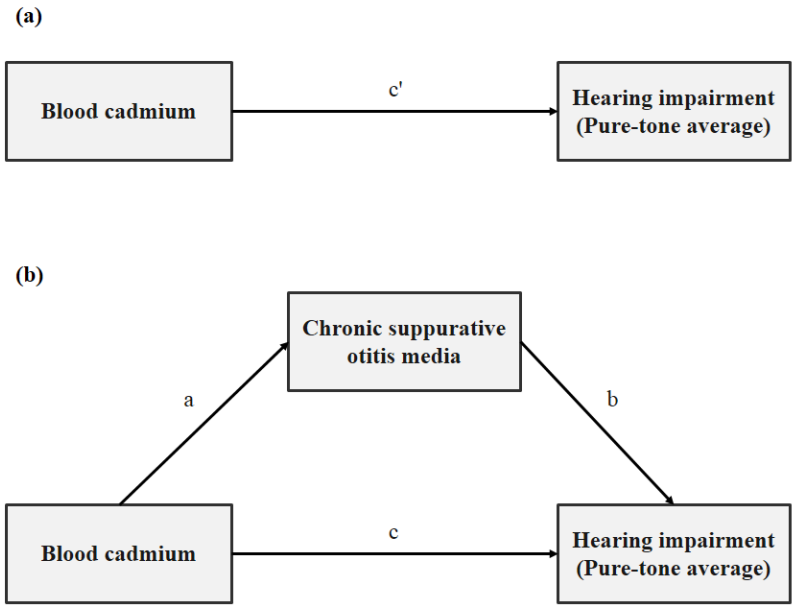

Table 1. Number of CSOM patients, GMs, 95% CIs of blood cadmium (μg/L) according to participant characteristics (n = 5838)

Characteristics	Non-CSOM participants [n (%)][a]	CSOM patients [n (%)][a]	*p* value[b]	Blood cadmium [GM (95% CI)]	*p* value[c]
Total	5838 (100.0)	164 (2.9)		0.91 (0.87 to 0.95)	
Sex					
Male	2785 (97.9)	69 (2.1)		0.75 (0.71 to 0.80)	
Female	2889 (96.4)	95 (3.6)	0.005	1.10 (1.04 to 1.17)	<0.001
Age, y					
20–39	2398 (98.9)	24 (1.1)		0.50 (0.47 to 0.53)	
40–54	1794 (96.5)	63 (3.5)		1.40 (1.32 to 1.49)	
55–70	1482 (94.3)	77 (5.7)	<0.001	1.61 (1.51 to 1.73)	<0.001
BMI, kg/m^2					
<25	3811 (97.2)	108 (2.8)		0.87 (0.83 to 0.92)	
≥25	1863 (97.0)	56 (3.0)	0.843	1.00 (0.93 to 1.07)	0.003
Smoking status					
Never	3489 (96.7)	107 (3.3)		0.80 (0.75 to 0.84)	
Former	845 (96.7)	30 (3.3)		0.70 (0.64 to 0.76)	
Current	1340 (98.3)	27 (1.7)	0.025	1.49 (1.39 to 1.59)	<0.001
Prevalence of CSOM					
No	5674 (100.0)	0 (0.0)		0.89 (0.85 to 0.94)	
Yes	0 (0.0)	164 (100.0)		1.77 (1.48 to 2.12)	<0.001
Hearing impairment					
No	5177 (97.8)	115 (2.2)		0.87 (0.83 to 0.91)	
Yes	497 (89.4)	49 (10.6)	<0.001	1.56 (1.36 to 1.79)	<0.001

BMI = body mass index; CI = confidence interval; CSOM = chronic suppurative otitis media; GM = geometric mean.

[a] Unweighted number and weighted percentages.

[b] Survey chi-squared test were performed

[c] Survey t-test for binominal groups and the Wald F-test for categorical groups.

Table 2. Odds ratios (95% confidence intervals) for CSOM according to blood concentration of cadmium

Blood cadmium (μg/L)	No. of participants	No. of CSOM patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.016 to 0.679)	1453	15	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.680 to 1.009)	1464	30	2.46 (1.21 to 5.03)*	1.78 (0.84 to 3.79)	1.96 (0.92 to 4.15)
Quartile 3 (1.010 to 1.452)	1463	62	5.83 (2.91 to 11.71)**	3.54 (1.62 to 7.75)*	4.19 (1.87 to 9.40)**
Quartile 4 (1.453 to 6.422)	1458	57	5.74 (2.88 to 11.44)**	3.08 (1.40 to 6.77)*	3.91 (1.72 to 8.86)*
P for trend			<0.001	<0.001	<0.001

CSOM = chronic suppurative otitis media
[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 3. Odds ratios (95% confidence intervals) for hearing impairment according to blood concentration of cadmium

Blood cadmium (μg/L)	No. of participants	No. of hearing impairment patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.016 to 0.679)	1453	60	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.680 to 1.009)	1464	127	2.4 (1.57 to 3.66)**	1.46 (0.91 to 2.35)	1.42 (0.88 to 2.31)
Quartile 3 (1.010 to 1.452)	1463	160	2.88 (1.96 to 4.25)**	1.38 (0.88 to 2.17)	1.32 (0.82 to 2.12)
Quartile 4 (1.453 to 6.422)	1458	199	3.86 (2.59 to 5.75)**	1.76 (1.11 to 2.79)*	1.66 (1.02 to 2.71)*
p for trend			<0.001	0.022	0.057

[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 4. PTA according to CSOM status in each ear

Group	No. of participants	Right ear		Left ear	
		CSOM status	PTA[b] (mean ± SE)	CSOM status	PTA[b] (mean ± SE)
1	5674	Normal	13.35 ± 0.20	Normal	13.18 ± 0.21
2	64	CSOM	36.45 ± 2.57**	Normal	22.60 ± 2.09**
3	60	Normal	17.39 ± 1.53*	CSOM	32.83 ± 2.51**
4	40	CSOM	27.33 ± 1.98**	CSOM	32.49 ± 3.30**

CSOM = chronic suppurative otitis media; PTA = pure tone average; SE = standard error
[a] Survey chi-square test was performed compared to Group 1.
[b] Survey t-test was performed compared to Group 1.
* $p < 0.05$
** $p < 0.001$

Table 5. Results of mediation analysis

Indirect effect	SE	*p* value[a]	Percent (%) of the total effect that is mediated
5.564	1.125	<0.001	5.00

[a] Sobel test was performed with the causal variable X as log transformed blood cadmium, mediator variable M as chronic suppurative otitis media status, and outcome variable Y as mean value of pure tone average in both ears.

Table 6. Odds ratios (95% confidence intervals) for CSOM according to blood concentration of cadmium after excluding participants with extreme values (GM±2SD) of blood cadmium

Blood cadmium (μg/L)	No. of participants	CSOM patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.296 to 0.707)	1386	15	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.708 to 1.024)	1396	31	2.05 (1.00 to 4.20)	1.53 (0.71 to 3.28)	1.68 (0.76 to 3.7)
Quartile 3 (1.025 to 1.451)	1387	60	4.77 (2.45 to 9.29)**	3.05 (1.45 to 6.41)*	3.67 (1.67 to 8.09)*
Quartile 4 (1.452 to 3.183)	1390	55	4.67 (2.30 to 9.50)**	2.65 (1.19 to 5.90)*	3.43 (1.43 to 8.23)*
p for trend			< 0.001	0.003	< 0.001

CSOM = chronic suppurative otitis media
[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 7. Odds ratios (95% confidence intervals) for hearing impairment according to blood concentration of cadmium after excluding participants with extreme values (GM±2SD) of blood cadmium.

Blood cadmium (μg/L)	No. of participants	No. of hearing impairment patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.296 to 0.707)	1386	67	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.708 to 1.024)	1396	126	2.08 (1.38 to 3.14)**	1.27 (0.82 to 1.97)	1.26 (0.81 to 1.95)
Quartile 3 (1.025 to 1.451)	1387	149	2.49 (1.67 to 3.72)**	1.26 (0.80 to 1.97)	1.22 (0.77 to 1.93)
Quartile 4 (1.452 to 3.183)	1390	190	3.29 (2.20 to 4.92)**	1.56 (1.01 to 2.42)*	1.50 (0.95 to 2.36)
p for trend			<0.001	0.050	0.093

[a] Model 1 was adjusted for age and sex.

[b] Model 2 was adjusted for age, sex, smoking status, and body mass index

* $p < 0.05$

** $p < 0.001$

Table 8. PTA according to CSOM status in each ear after excluding participants with extreme values (GM±2SD) of blood cadmium.

		Right ear			Left ear		
Group	No. of participants	CSOM status	Hearing impairment[a] [n (%)]	PTA[b] (mean ± SE)	CSOM status	Hearing impairment[a] [n (%)]	PTA[b] (mean ± SE)
1	5398	Normal	724 (11.4)	13.52 ± 0.21	Normal	760 (11.8)	13.37 ± 0.22
2	63	CSOM	38 (61.4)**	36.49 ± 2.60**	Normal	22 (32.1)**	22.53 ± 2.10**
3	58	Normal	11 (21.7)	17.03 ± 1.58*	CSOM	33 (51.8)**	32.93 ± 2.61**
4	40	CSOM	23 (49.8)**	27.33 ± 1.98**	CSOM	22 (46.1)**	32.49 ± 3.30**

CSOM = chronic suppurative otitis media; PTA = pure tone average; SE = standard error
[a] Survey chi-square test was performed compared to Group 1.
[b] Survey t-test was performed compared to Group 1.
* $p < 0.05$
** $p < 0.001$

Table 9. Results of Mediation Analysis after excluding participants with extreme values (GM±2SD) of blood cadmium

Indirect effect	SE	*p* value[a]	Percent (%) of the total effect that is mediated
6.078	1.292	<0.001	5.09

[a] Sobel test was performed with the causal variable X as log to transformed blood cadmium to mediator, variable M as chronic suppurative otitis media status, and outcome variable Y as mean value of pure to tone average in both ears.

Table 10. Odds ratios (95% confidence intervals) for CSOM according to blood concentration of cadmium after excluding former and current smoker participants

Blood cadmium (μg/L)	No. of participants	No. of CSOM patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.016 to 0.630)	890	9	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.631 to 0.959)	884	15	3.00 (1.22 to 7.36)*	2.04 (0.78 to 5.30)	2.04 (0.78 to 5.31)
Quartile 3 (0.960 to 1.423)	855	44	9.86 (4.28 to 22.73)**	5.35 (1.97 to 14.52)*	5.35 (1.97 to 14.55)*
Quartile 4 (1.424 to 6.422)	860	39	9.21 (4.01 to 21.13)**	4.33 (1.57 to 11.9)*	4.33 (1.56 to 12.00)*
p for trend			<0.001	0.004	0.004

CSOM = chronic suppurative otitis media

[a] Model 1 was adjusted for age and sex.

[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.

* $p < 0.05$

** $p < 0.001$

Table 11. Odds ratios (95% confidence intervals) for hearing impairment according to blood concentration of cadmium after excluding former and current smoker participants.

Blood cadmium (μg/L)	No. of participants	No. of hearing impairment patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.016 to 0.630)	890	19	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.631 to 0.959)	884	61	3.81 (1.95 to 7.47)**	2.21 (1.03 to 4.70)*	2.19 (1.03 to 4.67)*
Quartile 3 (0.960 to 1.423)	855	80	4.55 (2.45 to 8.46)**	2.00 (0.97 to 4.15)	2.00 (0.97 to 4.13)
Quartile 4 (1.424 to 6.422)	860	98	5.84 (3.03 to 11.24)**	2.24 (1.02 to 4.93)*	2.22 (1.01 to 4.87)*
p for trend			<0.001	0.159	0.167

[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 12. PTA according to CSOM status in each ear after excluding former and current smoker participants.

Group	No. of participants	Right ear			Left ear		
		CSOM status	Hearing impairment[a] [n (%)]	PTA[b] (mean±SE)	CSOM status	Hearing impairment[a] [n (%)]	PTA[b] (mean±SE)
1	3489	Normal	376 (9.1)	12.23 ± 0.24	Normal	389 (9.5)	12.13 ± 0.28
2	45	CSOM	31 (67.9)**	37.57 ± 2.81**	Normal	15 (30.5)**	21.27 ± 2.78*
3	37	Normal	6 (15.2)	15.34 ± 1.70	CSOM	20 (49.7)**	32.68 ± 3.15**
4	25	CSOM	13 (45.0)**	24.51 ± 1.65**	CSOM	12 (39.5)**	28.44 ± 1.85**

CSOM = chronic suppurative otitis media; PTA = pure tone average; SE = standard error
[a] Survey chi-square test was performed compared to Group 1.
[b] Survey t-test was performed compared to Group 1.
* $p < 0.05$
** $p < 0.001$

Table 13. Results of mediation analysis after excluding former and current smoker participants.

Indirect effect	SE	*p* value[a]	Percent (%) of the total effect that is mediated
6.772	1.388	<0.001	6.39

[a] Sobel test was performed with the causal variable X as log to transformed blood cadmium to mediator, variable M as chronic suppurative otitis media status, and outcome variable Y as mean value of pure to tone average in both ears.

Table 14. Odds ratios (95% confidence intervals) for CSOM according to blood concentration of cadmium after excluding participants aged 65 years or older.

Blood cadmium (μg/L)	No. of participants	No. of CSOM patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.016 to 0.665)	1369	13	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.667 to 0.994)	1370	27	2.70 (1.26 to 5.76)*	1.70 (0.77 to 3.74)	1.89 (0.86 to 4.13)
Quartile 3 (0.995 to 1.439)	1366	53	5.66 (2.66 to 12.04)**	2.89 (1.29 to 6.50)*	3.48 (1.52 to 7.95)*
Quartile 4 (1.440 to 6.422)	1374	53	5.73 (2.73 to 12.01)**	2.48 (1.09 to 5.63)*	3.19 (1.36 to 7.50)*
p for Trend			<0.001	0.005	0.001

CSOM = chronic suppurative otitis media
[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 15. Odds ratios (95% confidence intervals) for hearing impairment according to blood concentration of cadmium after excluding participants aged 65 years or older.

Blood cadmium (μg/L)	No. of participants	No. of hearing impairment patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.016 to 0.665)	899	19	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.667 to 0.994)	899	61	3.81 (1.95 to 7.47)**	2.21 (1.03 to 4.70)*	2.19 (1.03 to 4.67)*
Quartile 3 (0.995 to 1.439)	899	80	4.55 (2.45 to 8.46)**	2.00 (0.97 to 4.15)	2.00 (0.97 to 4.13)
Quartile 4 (1.440 to 6.422)	899	98	5.84 (3.03 to 11.24)**	2.24 (1.02 to 4.93)*	2.22 (1.01 to 4.87)*
p for trend			<0.001	0.015	0.017

[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 16. PTA according to CSOM status in each ear after excluding participants aged 65 years or older.

		Right ear			Left ear		
Group	No. of participants	CSOM status	Hearing impairment[a] [n (%)]	PTA[b] (mean±SE)	CSOM status	Hearing impairment[a] [n (%)]	PTA[b] (mean±SE)
1	5333	Normal	588 (9.8)	12.78 ± 0.21	Normal	610 (10.0)	12.56 ± 0.22
2	56	CSOM	33 (59.3)**	34.52 ± 2.91**	Normal	17 (27.0)**	20.49 ± 2.13**
3	55	Normal	10 (21.4)*	16.83 ± 1.64*	CSOM	29 (49.9)**	32.53 ± 2.68**
4	35	CSOM	21 (49.7)**	27.18 ± 1.78**	CSOM	19 (44.2)**	32.18 ± 3.47**

CSOM = chronic suppurative otitis media; PTA = pure tone average; SE = standard error
[a] Survey chi-square test was performed compared to Group 1.
[b] Survey t-test was performed compared to Group 1.
* $p < 0.05$
** $p < 0.001$

Table 17. Results of mediation analysis after excluding participants aged 65 years or older.

Indirect effect	SE	*p* value[a]	Percent (%) of the total effect that is mediated
0.252	0.052	<0.001	5.23%

[a] Sobel test was performed with the causal variable X as log to transformed blood cadmium to mediator, variable M as chronic suppurative otitis media status, and outcome variable Y as mean value of pure to tone average in both ears.

Table 18. Odds ratios (95% confidence intervals) for hearing impairment according to blood concentration of cadmium within participants with CSOM status.

Blood cadmium (μg/L)	No. of participants	No. of hearing impairment patients	Unadjusted Model	Model 1[a]	Model 2[b]
Quartile 1 (0.253 to 0.968)	40	8	1 (Referent)	1 (Referent)	1 (Referent)
Quartile 2 (0.977 to 1.210)	42	13	1.98 (0.61 to 6.39)	2.21 (1.03 to 4.70)	1.83 (0.58 to 5.71)
Quartile 3 (1.212 to 1.687)	41	14	1.79 (0.60 to 5.37)	2.00 (0.97 to 4.15)	1.37 (0.41 to 4.59)
Quartile 4 (1.692 to 4.871)	41	14	2.53 (0.83 to 7.73)	2.24 (1.02 to 4.93)	2.06 (0.59 to 7.23)
p for trend			0.156	0.180	0.405

[a] Model 1 was adjusted for age and sex.
[b] Model 2 was adjusted for age, sex, smoking status, and body mass index.
* $p < 0.05$
** $p < 0.001$

Table 19. Results of the linear regression analysis for mean value of PTA of both ears within participants with CSOM status.

	Coefficient	***p* value**
Blood cadmium concentration (log transformed)	1.347 ± 3.300	0.684
Age (years)	0.606 ± 0.106	<0.001
Sex (female)	-3.015 ± 3.481	0.388
Smoking	1.442 ± 2.026	0.478
Body mass index (kg/m^2)	-0.176 ± 0.452	0.697

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국문초록

카드뮴의 환경 노출, 만성화농성중이염, 그리고 청력 저하 사이의 연관성

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카드뮴은 다양한 용도로 사용되는 독성을 가진 중금속의 일종으로, 산화적 스트레스를 통해 다양한 독성을 나타내는 것이 알려져 있다. 최근 만성화농성중이염과 청력저하는 각각 산화적 스트레스와 관련되어 있다는 것이 연구되어 왔다. 하지만 카드뮴, 만성화농성중이염, 청력저하 사이의 연관성에 대하여는 거의 연구되어 있지 않다. 이 연구의 목적은 환경적인 카드뮴 노출이 성인에서 청력저하를 일으키고, 그 매개단계로 만성화농성중이염이 작용하는지 알아보기 위함

에 있다.

본 연구는 단면조사연구로, 2009년부터 2012년까지 수행된 국민건강영양조사 제 4기 및 제 5기, 제 6기의 자료 중 혈중 카드뮴 농도가 측정된 20-69세의 성인 5,838명을 대상으로 수행되었다. 만성화농성중이염은 이비인후과적 검진을 통하여 진단되었으며, 청력저하는 건측 귀에서 0.5, 1, 2, 4kHz의 순음청력역치의 평균이 25dB을 초과하는 경우로 정의되었다.

조사설계의 가중치를 고려한 대상 연구집단의 만성화농성중이염의 유병율은 2.9%였으며, 청력저하인 연구대상자는 7.7%였다. 나이, 성별, 흡연유무, 체질량지수를 보정한 후 혈중 카드뮴 농도가 가장 낮은 사분위수군과 비교하였을 때 가장 높은 사분위수군의 만성화농성중이염 유병 여부에 대한 오즈비는 3.91배(신뢰구간 1.72 – 8.86)로 통계적으로 유의한 차이를 보였다. 같은 방법으로 산출한 청력저하에 대한 오즈비는 1.66배(신뢰구간 1.02 – 2.71)로 역시 통계적으로 유의한 차이를 보였다. 만성화농성중이염이 혈중 카드뮴 농도와 청력저하 사이에서 매개역할을 하는지 알아보기 위해 수행한 Sobel test에서 매개하는 분율은 5%로 나타났으며, 통계적으로 유의한 결과를 보였다(Sobel = 5.564, $p < 0.001$).

본 연구는 환경적인 카드뮴 노출이 만성화농성중이염과 청력저하와 연관성이 있음을 살펴보았고, 그 과정에서 만성화농성중이염이 매개역할을 함을 알아보았다. 환경적인 카드뮴 노출에 대한 또다른 건강영향을 나타내는 연구로 앞으로 이에 대한 추가적인 연구들이 더 필요할 것으로 생각된다.

주요어 : 카드뮴, 중이염, 화농성, 청력저하

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