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Association Between Hearing Impairment and Albuminuria in the Korean Adults

The 2011–2012 Korea National Health and Nutrition Examination Survey

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Abstract: Although the associations between albuminuria and renal and cardiovascular diseases, including diabetes and hypertension, have been extensively studied, few studies have investigated the association between albuminuria and hearing impairment. In this study, we assessed the relationship between albuminuria and hearing impairment in 9786 adult Korean subjects, using data from the Korea National Health and Nutrition Examination Survey (KNHANES) performed in 2011–2012. The range of urinary albumin-to-creatinine ratio (UACR) was divided into 4 grades: grade 1 (first tertile of low-grade albuminuria [LGA]), 0.00 to 1.99 mg/g Cr; grade 2 (second tertile of LGA), 2.00 to 5.49 mg/g Cr; grade 3 (third tertile of LGA), 5.50 to 29.99 mg/g Cr; grade 4 (albuminuria), ≥ 30.00 mg/g Cr.

The age- and sex-adjusted weighted UACR was higher in subjects with hearing impairment compared with those without hearing impairment (26.2 ± 4.7 mg/g Cr vs 14.1 ± 1.5 mg/g Cr, $P = 0.020$). The age- and sex-adjusted weighted prevalence of albuminuria was also higher in subjects with hearing impairment compared with subjects without hearing impairment ($8.3 \pm 0.9\%$ vs $5.8 \pm 0.4\%$, $P = 0.013$). The age- and sex-adjusted weighted percentage of hearing impairment increased as UACR increased ($18.0\% \pm 0.6\%$, $20.0\% \pm 0.8\%$, $22.2\% \pm 0.9\%$, $25.3\% \pm 2.0\%$, respectively; $P < 0.001$). Logistic regression analyses were performed for hearing impairment by albuminuria, with age, sex, tobacco use, heavy alcohol use, educational background, occupational noise exposure, obesity, hypertension, diabetes, total serum cholesterol, and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² as covariates. Using grade 1 of UACR as the control, grade 3 (odds ratio [OR] 1.28, 95% confidence interval [CI] 1.05–1.53, $P = 0.005$) and grade 4 (OR 1.41, 95% CI 1.04–1.90, $P = 0.026$) of UACR were correlated with hearing impairment, respectively. When the level of hearing impairment (dB) was analyzed as a continuous variable, it was positively correlated with log UACR (Spearman correlation, unadjusted $r = 0.226$, adjusted $r = 0.076$, $P < 0.001$).

In conclusion, we are the first to demonstrate that albuminuria is associated with hearing impairment in the Korean general population,

using nationally representative data. Screening for albuminuria would allow for interventions for the prevention of hearing impairment.

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Abbreviations: BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, FPG = fasting plasma glucose, KNHANES = Korea National Health and Nutrition Examination Survey, UACR = urinary albumin-to-creatinine ratio, LGA = low-grade albuminuria, OR = odds ratio, TG = triglyceride.

INTRODUCTION

Hearing impairment is currently one of the most common health conditions, with prevalence continuing to increase because of an aging society.^{1,2} According to the World Health Organization (WHO), worldwide, 360 million people and approximately one-third of people over 65 years of age are affected by disabling hearing loss.³ We reported recently that the overall prevalence of hearing impairment among the Korean adults (≥ 19 years' old) was 20.5%, using data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2010–2012 study.⁴ Furthermore, the prevalence of hearing loss for adults aged 65 years and older increased to about 70%.⁴

Traditionally, hearing impairment has been known to be associated with male sex, industrial or military occupation, noise exposure, and low socioeconomic status, as well as older age.^{5–8} Cardiovascular disease (CVD) and its risk factors have often been thought to contribute to hearing impairment, at least through the effect of CVD on the stria vascularis, which is important for maintaining normal signal transduction in the inner ear.^{9,10} There have been a few researches into an association between cardiovascular risk factors and the risk of hearing impairment.^{11–14} In a previous study, we also found that subjects with cardiovascular risk factors, such as smoking, hypertension, diabetes, increased total serum cholesterol, and decreased estimated glomerular filtration rate (eGFR) are especially at greater risk of hearing impairment.⁴

Meanwhile, the association between the risk of cardiovascular disease and albuminuria is well known. Albuminuria is an indicator of insulin resistance and of the increased renal and cardiovascular risks associated with metabolic syndrome.¹⁵ The Heart Outcomes Prevention Evaluation (HOPE) study found that any degree of albuminuria is a risk factor for cardiovascular events in individuals with or without diabetes.¹⁶ Urinary albumin excretion is also a predictor of cardiovascular mortality in general population.¹⁷

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Because cardiovascular risk factors increased the risk of hearing impairment, we speculated that there was a relationship between albuminuria and hearing impairment, based on cardiovascular risk factors.

Therefore, we investigated the association between hearing impairment and albuminuria in the Korean adult population using the data from the 2011–2012 KNHANES.

METHODS

Study Population and Data Collection

This study is based on data from the 2011–2012 KNHANES, a cross-sectional and nationally representative survey conducted by the Korea Centers for Disease Control and Prevention. The KNHANES has been conducted periodically since 1998 to assess the health and nutritional status of the civilian, noninstitutionalized population of Korea. Participants were selected using proportional allocation-systemic sampling with multistage stratification. A standardized interview was conducted in the homes of the participants to collect information on demographic variables, family history, medical history, medications used, and a variety of other health-related variables. The Health Interview included an established questionnaire to determine the demographic and socioeconomic characteristics of the subjects including age, education level, occupation, income, marital status, smoking habits, alcohol consumption, exercise, previous and current diseases, and family disease history.

Subjects were asked whether they exercise with an intensity that leaves them sweating or with a light difficulty in breathing. Subjects who exercised regularly and at a moderate intensity were asked about the frequency with which they exercised per week and the length of time per exercise session. Regular exercise was defined as exercising ≥ 5 times per week. Alcohol consumption was assessed by questioning the subjects about their drinking behavior during the month before the interview. Heavy alcohol use was categorized as drinking ≥ 4 times per week during the month before the interview. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medications irrespective of blood pressure. Diabetes was defined by fasting plasma glucose (FPG) ≥ 7.0 mmol/L, current antidiabetes medication, or a previous diagnosis of diabetes by a physician. Obesity was defined as body mass index (BMI) ≥ 25.0 kg/m² according to the Asia-Pacific obesity classification.¹⁸

Height and weight were obtained using standardized techniques and equipment. Height was measured to the nearest 0.1 cm using a portable stadiometer (Seriter, Bismarck, ND). Weight was measured to the nearest 0.1 kg using a Giant-150N calibrated balance-beam scale (Hana, Seoul, Korea). BMI was calculated by dividing weight by the square of their height (kg/m²). Systolic and diastolic blood pressures were measured by standard methods using a sphygmomanometer while the patient was seated. Three measurements were recorded for all subjects at 5-minute intervals, and the average of the second and third measurements was used in the analysis.

Audiometric Measure

In the 2011–2012 KNHANES, the audiometric examination was administered to adults, aged 19 years or older. Air-conduction pure-tone thresholds were obtained in a soundproof booth using an automatic audiometer (GSI SA-203; Entomed Diagnostics AB, Lena Nodin, Sweden). Trained otolaryngologists collected data independently for each ear at 6 frequencies;

0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 kHz. All audiometric testing was performed under the supervision of an otolaryngologist. To obtain reliable results from the survey, the Epidemiologic Survey Committee of the Korean Society of Otorhinolaryngology-Head and Neck Surgery carried out the quality control of the survey, which was conducted by periodic education of participating otolaryngologists.

We determined hearing impairment for 2 categories of frequency (low/mid, high) and severity (mild, moderate-to-profound). To produce low/mid frequency pure tone means, we averaged the pure-tone hearing thresholds measured at 0.5, 1.0, and 2.0 kHz for each ear. To produce high-frequency pure tone means, we averaged the pure-tone hearing thresholds measured at 3.0, 4.0, and 6.0 kHz for each ear.

Mild hearing impairment was defined as an unaided pure-tone hearing threshold level for the superior ear of 26 to 40 decibels (Db), and average hearing threshold levels (HL) for the frequencies of 0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 kHz. Moderate-to-profound hearing impairment was defined as unaided pure-tone hearing threshold level for the superior ear of ≥ 40 Db, and average hearing threshold levels (HL) for the frequencies of 0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 kHz.

Laboratory Methods

Blood samples were collected in the morning after fasting for at least 8 hours. Total cholesterol, FPG, triglyceride (TG), and serum creatinine levels were measured by Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Urine albumin and creatinine concentrations were measured in the same laboratory for all surveys. Serum and urinary concentrations of creatinine were measured using a colorimetric method (Hitachi Automatic Analyzer 7600, Hitachi). The interassay coefficient of variation for serum creatinine was $<1.4\%$. Urinary albumin was measured in random urine samples using a turbidimetric immunoassay (Hitachi Automatic Analyzer 7600, Hitachi). Laboratory control measures used in the KNHANES indicated that these assays were highly reliable with consistently low coefficients of variation (3.1%). Urinary albumin-to-creatinine ratio (UACR) was reported as the albumin-creatinine ratio in milligrams per gram of creatinine (mg/g Cr). The cutoff level for albuminuria was ≥ 30 mg/g Cr (microalbuminuria was defined as UACR = 30–299 mg/g Cr, and macroalbuminuria was defined as UACR ≥ 300 mg/g Cr).¹⁹ UACR levels <30 mg/g Cr, previously considered to be in the normal range, were defined as low-grade albuminuria (LGA).²⁰ Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times (S_{Cr}/88.4, \mu\text{mol/L})^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$.²¹

Definitions

The range of UACR was divided into 4 grades: grade 1 (first tertile of LGA), 0.00 to 1.99 mg/g Cr; grade 2 (second tertile of LGA), 2.00 to 5.49 mg/g Cr; grade 3 (third tertile of LGA), 5.50 to 29.99 mg/g Cr; grade 4 (albuminuria), ≥ 30.00 mg/g Cr.

Ethics statement

This study was approved by the institutional review board of Ilsan Paik Hospital, Republic of Korea. After approval of the study proposal, the KNHANES dataset was made available at the request of the investigator. Because the dataset did not include any personal information and participants' consent had

already been given for the KNHANES, our study was exempt from requiring participant consent.

Statistical Analyses

The KNHANES participants were not randomly sampled. The survey was designed using a complex, stratified, multi-stage probability-sampling model; thus, individual participants were not equally representative of the Korean population. To obtain representative prevalence rates from the dataset, it was necessary to consider the power of each participant (sample weight) as representative of the Korean population. Following approval from the Korea Centers for Disease Control and Prevention, we received a survey dataset that included information regarding the survey location, strata by age, sex, and various other factors, and the sample weight for each participant. The survey sample weights, which were calculated by taking into account the sampling rate, response rate, and age/sex proportions of the reference population (2005 Korean National Census Registry), were used in all of the analyses to provide representative estimates of the noninstitutionalized Korean civilian population.

To compare the age- and sex-adjusted weighted clinical characteristics by the presence of hearing impairment, an analysis of covariance (ANCOVA) test was used. We compared the weighted and adjusted prevalence of hearing impairment among the 4 albuminuria groups (tertiles of UACR <30 mg/g Cr and albuminuria) with age, sex, tobacco use, heavy alcohol use, educational background, occupational noise exposure, obesity, hypertension, diabetes, total serum cholesterol, and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² as covariates, using an ANCOVA test. To examine the association between the level of hearing impairment (dB) as a continuous variable and log-transformed UACR, unweighted Spearman correlation tests were performed (unadjusted and adjusted for the above-mentioned variables). A logistic regression analysis was used to evaluate the odds ratios (ORs) for hearing impairment by the degree of albuminuria (tertiles of UACR <30 mg/g Cr and albuminuria) with the above-mentioned variables as covariates. All of the tests were 2-sided, and *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (ver. 21.0 for Windows; SPSS, Chicago, IL).

RESULTS

Demographics and Clinical Characteristics of the Study Population

The weighted demographics and clinical characteristics of study population are presented in Table 1.

Among 12,859 adults (≥19 years' old) who participated in the 2011–2012 KNHANES, a total of 10,948 subjects completed the audiometric test. Among 10,948 adults, 1212 subjects were excluded who did not complete laboratory tests including fasting plasma glucose and albuminuria. The remaining 9786 participants (weighted *n* = 31,462,075) were analyzed in this study.

The mean age of participants was 45.6 years, and the percentage of women was 47.0%. The prevalence of hypertension and diabetes were 26.3% and 8.7%, respectively. The percentage of occupational noise exposure and current tobacco use were 13.8% and 26.9%, respectively.

The prevalences of microalbuminuria and macroalbuminuria were 5.5% and 0.8%, respectively. The mean UACR was 16.5 mg/g Cr.

TABLE 1. Weighted Clinical Characteristics of Study Population (Unweighted, *n* = 9786; Weighted, *n* = 31,462,075)

	Mean (95% CI)
Age, y	45.6 (45.0–46.2)
Women (%)	47.0 (46.0–48.1)
Current smoking (%)	26.9 (25.6–28.1)
Heavy alcohol drinking (%)	7.5 (6.8–8.2)
Occupation noise exposure (%)	13.8 (12.7–15.0)
College graduation (%)	31.8 (30.1–33.5)
Body mass index, kg/m ²	23.8 (23.7–23.9)
Obesity (%)	33.1 (31.7–34.4)
Systolic blood pressure, mmHg	117.9 (117.4–118.4)
Diastolic blood pressure, mmHg	76.3 (75.9–76.6)
Hypertension (%)	26.3 (25.0–27.6)
Serum total cholesterol, mg/dL	189.4 (188.4–190.5)
Serum triglyceride, mg/dL	135.5 (132.3–138.7)
Fasting plasma glucose, mg/dL	97.0 (96.4–97.5)
Diabetes (%)	8.7 (8.0–9.4)
eGFR <60 mL/min/1.73 m ² (%)	2.9 (2.6–3.3)
Urinary albumin-to-creatinine ratio	16.5 (13.9–19.2)
Microalbuminuria (%)	5.5 (4.9–6.1)
Macroalbuminuria (%)	0.8 (0.7–1.1)

eGFR = estimated glomerular filtration rate; occupational noise exposure = a history of loud noise at work that required speaking in a loud voice to be heard >3 months.

Overall, the weighted prevalence of mild and moderate-to-profound hearing impairment among the Korean population were 10.4% (95% CI [9.7–11.1], *n* = 3267,088/31,462,075) and 9.8% (95% CI [9.0–10.6], *n* = 3,080,848/31,462,075), respectively.

Age- and Sex-Adjusted Clinical Characteristics by the Presence of Hearing Impairment

Age- and sex-adjusted clinical characteristics according to the presence of hearing impairment are shown in Table 2.

The percentage of occupational noise exposure, antihypertensive drug use, the presence of hypertension, antidiabetes drug use, eGFR <60 mL/min/1.73 m², and the presence of albuminuria were higher in adults with hearing impairment, compared with adults without hearing impairment. However, the levels of total serum cholesterol and TG, BMI, and the percentage of college graduation were lower in subjects with hearing impairment compared with subjects without hearing impairment. UACR was higher in adults with hearing impairment compared with adults without hearing impairment (26.2 ± 4.7 vs 14.1 ± 1.5 mg/g Cr, *P* = 0.020). The prevalence of albuminuria was also higher in subjects with hearing impairment compared with subjects without hearing impairment. (8.3% ± 0.9% vs 5.8% ± 0.4%, *P* = 0.013).

Weighted Adjusted Prevalence of Hearing Impairment by the Degree of UACR

The weighted adjusted prevalence of hearing impairment by the degree of UACR are shown according to the severity and frequency of hearing impairment in Table 3. The age- and sex-adjusted weighted percentage of hearing impairment increased as UACR increased (18.0% ± 0.6%, 20.0% ± 0.8%, 22.2% ± 0.9%,

TABLE 2. Weighted, Age- and Sex-Adjusted Demographic and Clinical Characteristics By the Presence of Hearing Impairment in Korean Adults, Aged 19 Years and Older (2011–2012 KNHANES)

	Normal (Weighted n = 25,114,139)	Impaired (Weighted n = 6,347,936)	P
Age, y	41.5 ± 0.2	61.9 ± 0.4	<0.001
Women (%)	47.0 ± 1.0	48.0 ± 1.0	0.679
Current smoking (%)	26.6 ± 0.7	27.8 ± 1.3	0.444
Heavy alcohol drinking (%)	7.2 ± 0.4	8.5 ± 0.9	0.213
College graduation (%)	34.2 ± 0.9	22.2 ± 1.2	<0.001
Occupational noise exposure (%)	13.2 ± 0.1	16.3 ± 0.1	0.017
Body mass index, kg/m ²	23.9 ± 0.1	23.5 ± 0.1	<0.001
Waist circumference, cm	81.7 ± 0.2	81.0 ± 0.3	0.059
Obesity (%)	34.0 ± 0.8	29.3 ± 1.4	0.002
Systolic blood pressure, mmHg	117.9 ± 0.2	118.0 ± 0.5	0.858
Diastolic blood pressure, mmHg	76.9 ± 0.2	74.0 ± 0.4	<0.001
Anti-hypertensive drug (%)	13.5 ± 0.1	19.8 ± 0.1	<0.001
Hypertension (%)	26.0 ± 0.7	29.0 ± 1.4	0.034
Serum total cholesterol, mg/dL	190.4 ± 0.6	185.4 ± 1.2	<0.001
Serum triglyceride, mg/dL	137.7 ± 1.8	126.9 ± 3.5	0.007
Anti-lipid drug	4.8 ± 0.3	4.8 ± 0.8	0.991
Fasting plasma glucose, mg/dL	97.1 ± 0.3	96.6 ± 0.7	0.504
Anti-diabetes drug (%)	4.8 ± 0.3	7.5 ± 0.8	0.005
Diabetes (%)	8.0 ± 0.4	10.0 ± 0.9	0.104
eGFR <60 mL/min/1.73 m ² (%)	2.3 ± 0.2	5.1 ± 0.6	<0.001
Urinary albumin-to-creatinine ratio, mg/g Cr	14.1 ± 1.5	26.2 ± 4.7	0.020
Albuminuria (%)	5.8 ± 0.4	8.3 ± 0.9	0.013

Data are expressed as mean ± standard error mean. The estimates for age and sex are not adjusted. eGFR = estimated glomerular filtration rate.

25.3% ± 2.0%, respectively; $P < 0.001$). This trend persisted after adjusting for current smoking, heavy alcohol drinking, educational background, occupational noise exposure, obesity, diabetes, hypertension, serum total cholesterol, and eGFR <60 mL/min/1.73 m². According to the frequency of hearing impairment, the age- and sex-adjusted weighted percentage of low/mid frequency hearing impairment in grade 1 of UACR was lower than in grade 3 or 4 of UACR ($P = 0.005$). This trend did not persist after adjusting for current smoking, heavy alcohol drinking, educational background, occupational noise exposure, obesity, diabetes, hypertension, serum total cholesterol, and

eGFR <60 mL/min/1.73 m². The weighted percentage of high-frequency hearing impairment also did not show any difference according to the range of albuminuria.

According to severity of hearing impairment, for moderate-to-profound hearing impairment, the age- and sex-adjusted weighted percentage of hearing impairment in grade 1 of UACR was lower than in grade 3 or 4 of UACR in both the low/mid and high frequencies. This trend persisted after adjusting for current smoking, heavy alcohol drinking, educational background, occupational noise exposure, obesity, diabetes, hypertension, serum total cholesterol, and eGFR <60 mL/min/1.73 m². However, the weighted adjusted prevalence of mild hearing impairment by range of albuminuria did not show any difference.

The Association Between Hearing Impairment and Albuminuria by the Degree of UACR

In the logistic regression analysis for hearing impairment by albuminuria, we adjusted for age, sex, current smoking, heavy alcohol drinking, education level, occupational noise exposure, obesity, hypertension, diabetes, serum total cholesterol, and eGFR <60 mL/min/1.73 m² (Table 4).

Using grade 1 of UACR as the control, grade 3 (OR 1.28, 95% CI 1.05–1.53, $P = 0.005$) and grade 4 (OR 1.41, 95% CI 1.04–1.90, $P = 0.026$) of UACR were both correlated with hearing impairment.

According to severity of hearing impairment, albuminuria did not increase the risk of mild hearing impairment. However, grade 3 (OR 1.31, 95% CI 1.04–1.66, $P = 0.022$) and grade 4 (OR 1.51, 95% CI 1.10–2.08, $P = 0.011$) of UACR increased the risk of moderate-to-profound hearing impairment, using grade 1 of UACR as the control.

According to the frequency of moderate-to-profound hearing impairment, grades 3 and 4 of UACR, with grade 1 of UACR as the control, increased the risk of both low/mid and high frequency hearing impairment.

When the level of hearing impairment (dB) was analyzed as a continuous variable, it was positively correlated with log UACR (Spearman correlation, unadjusted $r = 0.226$, adjusted $r = 0.076$, $P < 0.001$) (Fig. 1).

DISCUSSION

This is the first study to demonstrate that albuminuria was associated with hearing impairment in the Korean population aged 19 years or older, after adjusting for confounding factors including diabetes, hypertension and eGFR <60 mL/min/1.73 m² using nationally representative data.

In a previous study, we reported that hearing impairment in Korea was extremely prevalent and that the risks of hearing impairment among individuals with cardiovascular risk factors were exacerbated in some groups, such as those of advanced age, with low socioeconomic status, and/or having occupational noise exposure.⁴

In this study, we also found that subjects with hearing impairment demonstrated a greater percentage of antihypertensive drug use, the presence of hypertension, antidiabetes drug use, eGFR <60 mL/min/1.73 m², and the presence of albuminuria, compared with subjects without hearing impairment. Because albuminuria is thought to be a marker of cardiovascular risk factors, we thought that there was a link between hearing impairment and albuminuria. Although the associations between albuminuria and renal and cardiovascular diseases, including diabetes and hypertension, have been extensively

TABLE 3. Weighted, Multivariable-Adjusted Prevalence of Hearing Impairment According to the Severity and Frequency By the Degree of Albuminuria in Korean Adults

Range of Urinary albumin-to-Creatinine Ratio, mg/g Cr	Low-Grade Albuminuria			Albuminuria	P for Trend
	Grade 1 Tertile 1 0–1.99	Grade 2 Tertile 2 2.00–5.49	Grade 3 Tertile 3 5.50–29.99	Grade 4 30.00–	
N, (unweighted/weighted)	3,314/11,036,009	3,223/11,161,528	2,466/7,276,629	783/1,987,909	
Mild or greater					
Whole range frequency impairment					
Model 1	18.0 ± 0.6	20.0 ± 0.8	22.2 ± 0.9	25.3 ± 2.0	<0.001
Model 2	18.5 ± 0.5	20.3 ± 0.8	21.7 ± 0.9	23.6 ± 2.1	0.009
Mild or greater					
Low/mid frequency impairment					
Model 1	15.0 ± 0.6	16.3 ± 0.7	18.1 ± 0.8	20.4 ± 1.7	0.005
Model 2	15.4 ± 0.6	16.5 ± 0.7	17.5 ± 0.8	18.6 ± 1.8	0.152
Mild or greater					
High frequency impairment					
Model 1	33.9 ± 0.9	35.5 ± 0.9	36.9 ± 1.1	38.3 ± 1.7	0.085
Model 2	34.5 ± 0.8	35.7 ± 0.9	36.0 ± 1.1	36.7 ± 1.8	0.606
Mild					
Whole range frequency impairment					
Model 1	9.6 ± 0.5	10.7 ± 0.6	11.1 ± 0.8	10.9 ± 1.6	0.243
Model 2	9.8 ± 0.5	10.7 ± 0.6	10.8 ± 0.8	10.2 ± 1.7	0.542
Mild					
Low/mid frequency impairment					
Model 1	7.8 ± 0.4	8.8 ± 0.5	8.6 ± 0.6	6.2 ± 1.3	0.215
Model 2	8.1 ± 0.4	8.9 ± 0.5	8.3 ± 0.6	5.3 ± 1.3	0.0110
Mild					
High frequency impairment					
Model 1	12.3 ± 0.7	12.1 ± 0.6	10.9 ± 0.8	9.8 ± 1.5	0.274
Model 2	12.5 ± 0.7	12.2 ± 0.6	10.6 ± 0.8	9.7 ± 1.6	0.162
Moderate-to-profound					
Whole range frequency impairment					
Model 1	8.5 ± 0.5	9.4 ± 0.6	11.1 ± 0.7	14.4 ± 1.5	<0.001
Model 2	8.6 ± 0.5	9.6 ± 0.6	10.9 ± 0.7	13.4 ± 1.6	0.011
Moderate-to-profound					
Low/mid frequency impairment					
Model 1	7.2 ± 0.5	7.5 ± 0.6	9.4 ± 0.7	14.1 ± 1.5	<0.001
Model 2	7.4 ± 0.5	7.7 ± 0.6	9.2 ± 0.7	13.2 ± 1.6	0.005
Moderate-to-profound					
High frequency impairment					
Model 1	23.3 ± 0.7	25.6 ± 0.8	27.3 ± 0.9	30.2 ± 1.9	0.001
Model 2	23.8 ± 0.7	25.8 ± 0.8	26.7 ± 0.9	28.5 ± 1.9	0.041

Mild hearing impairment: unaided pure-tone hearing threshold level for the better ear of 26 to 40 decibels (Db), average of the hearing threshold levels (HL) for the frequencies of 0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 kHz. Moderate-to-profound hearing impairment: unaided pure-tone hearing threshold level for the better ear of 40 Db or greater, average of the hearing threshold levels (HL) for the frequencies of 0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 kHz. Low/mid frequency mild hearing impairment: pure tone average >25 Db hearing level measured at 0.5, 1.0, and 2.0 kHz for each individual and ear. High frequency mild hearing impairment: pure tone average >25 Db hearing level measured at 3.0, 4.0, and 6.0 kHz for each individual and ear. Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, current smoking, heavy alcohol drinking, educational background, occupational noise exposure, obesity, diabetes, hypertension, eGFR <60 mL/min/1.73 m², and serum total cholesterol.

studied, few studies have investigated the association between albuminuria and hearing impairment.

Most studies concerning the relationship between albuminuria and hearing impairment have been performed mainly in subjects with diabetes. Several researchers reported that diabetic patients had a higher prevalence of hearing impairment

than healthy subjects.^{14,22,23} Shen et al²⁴ showed that increased albuminuria was positively associated with the severity of hearing impairment in patients with type 2 diabetes mellitus.

However, we found that age- and sex-adjusted weighted prevalence of hearing impairment showed a significant difference according to the degree of albuminuria in a general

TABLE 4. Logistic Regression Models to Predict the Risk of Hearing Impairment by the Degree of Albuminuria in Korean Adults

Albuminuria	Odds Ratio (95% CI)	P
Mild or greater whole range frequency impairment		
Grade 1	Reference	
Grade 2	1.13 (0.94–1.37)	0.198
Grade 3	1.28 (1.08–1.53)	0.005
Grade 4	1.41 (1.04–1.90)	0.026
Mild or greater low/Mid frequency impairment		
Grade 1	Reference	
Grade 2	1.08 (0.88–1.32)	0.464
Grade 3	1.20 (0.99–1.45)	0.058
Grade 4	1.24 (0.94–1.64)	0.127
Mild or greater high frequency impairment		
Grade 1	Reference	
Grade 2	1.03 (0.87–1.23)	0.717
Grade 3	1.11 (0.91–1.35)	0.298
Grade 4	1.20 (0.90–1.59)	0.211
Mild whole range frequency impairment		
Grade 1	Reference	
Grade 2	1.10 (0.92–1.32)	0.307
Grade 3	1.13 (0.92–1.40)	0.249
Grade 4	1.08 (0.79–1.47)	0.640
Mild low/Mid frequency impairment		
Grade 1	Reference	
Grade 2	1.11 (0.90–1.38)	0.334
Grade 3	1.06 (0.85–1.31)	0.619
Grade 4	0.79 (0.58–1.07)	0.121
Mild high frequency impairment		
Grade 1	Reference	
Grade 2	0.97 (0.80–1.17)	0.728
Grade 3	0.88 (0.72–1.09)	0.233
Grade 4	0.85 (0.63–1.14)	0.269
Moderate to profound whole range frequency impairment		
Grade 1	Reference	
Grade 2	1.11 (0.85–1.46)	0.447
Grade 3	1.31 (1.04–1.66)	0.022
Grade 4	1.51 (1.10–2.08)	0.011
Moderate to profound low/mid frequency impairment		
Grade 1	Reference	
Grade 2	1.02 (0.77–1.35)	0.915
Grade 3	1.28 (1.00–1.63)	0.050
Grade 4	1.69 (1.21–2.37)	0.002
Moderate to profound High frequency impairment		
Grade 1	Reference	
Grade 2	1.10 (0.91–1.33)	0.341
Grade 3	1.21 (1.01–1.45)	0.043
Grade 4	1.34 (1.01–1.78)	0.041

All odds ratios were from weighted analyses. The range of albuminuria (urinary albumin-to-creatinine ratio) was divided into 4 grades: Grade 1 (first tertile of low-grade albuminuria [LGA]), 0.00–1.99 mg/g Cr; Grade 2 (second tertile of LGA), 2.00–5.49 mg/g Cr; Grade 3 (third tertile of LGA), 5.50–29.99 mg/g Cr; Grade 4 (albuminuria), ≥ 30.00 mg/g Cr. Analyses were performed with age, sex, tobacco use, heavy alcohol use, educational background, occupational noise exposure, obesity, hypertension, diabetes, total serum cholesterol, and eGFR < 60 mL/min/1.73 m² as covariates.

population, even after adjusting diabetes. The association between hearing impairment and albuminuria existed in moderate-to-profound hearing impairment, regardless of the frequency. Furthermore, the log-transformed level of albuminuria was also positively correlated with the severity of hearing impairment in the general population.

We speculated that an angiopathic mechanism involving atherosclerosis contributed to the link between albuminuria and hearing impairment.

Albuminuria may simply represent the consequence of increased glomerular pressure, such as that due to hypertension. However, albuminuria is often considered a marker of the increased risk of atherosclerotic cardiovascular disease associated with oxidative stress, increased circulating inflammatory factors, and endothelial dysfunction.¹⁵ A recent prospective study showed that albuminuria was associated with vascular events and displayed a myocardial infarction risk equivalent, independently of traditional cardiovascular risk factors.²⁵

On the contrary, hearing function can be at risk as a result of even minor vascular changes, because the inner ear, especially the stria vascularis, requires an uncompromised local blood flow and the cochlear vasculature is very sensitive to circulating inflammatory factors.⁹ The most important cause of neuronal degeneration is atherosclerosis, which may diminish the vascularity of the cochlea, thereby reducing its oxygen supply and leading to hearing impairment.²⁶ Actually, carotid intima-media thickness or plaque and flow-mediated dilation of the brachial artery, early indices of subclinical atherosclerosis, have been associated with hearing impairment.^{27,28} Furthermore, a recent study showed that the angiographic severity and extent of coronary artery disease are significantly correlated with the degree of hearing loss.²⁹ Peter et al³⁰ also reported that women with a self-reported history of myocardial infarction were twice as likely to have cochlear impairment as women without a history of myocardial infarction.

Taken together, albuminuria, a known risk factor of CVD, may be the indicator of atherosclerosis, which has an important role in the development of hearing impairment.

In this study, even in subjects with UACR levels < 30 mg/g Cr, previously considered to be in the normal range, the third tertile of LGA increased the risk of hearing impairment compared to the first tertile of LGA. In the association between albuminuria and cardiovascular risk, recent findings have indicated that LGA is associated with cardiovascular morbidity and mortality in the general population.^{17,31,32} Therefore, the relationship between albuminuria and hearing impairment via the mechanism involving atherosclerosis begins at the subnormal range of albuminuria, as early as the association between albuminuria and CVD.

There have been other explanations suggested for the pathologic mechanisms that may be shared by the renal and otological systems. First, there are some proteins, such as claudins, which are tight junction proteins that play a key role in the cell-to-cell communication, in both ear and kidney tissues. Genetic or acquired damage in these proteins might deteriorate the function of kidney and ear concurrently.³³ There are also interesting links between kidney disease and hearing impairment, such as those in Alport syndrome, Pendred syndrome, and Branchio-otorenal syndrome.³³ However, there is a limitation in that each of the kidney diseases mentioned above is not characterized by albuminuria. Second, the cochlea and glomerulus have common physiological mechanisms, specifically, the active transport of fluid and electrolytes by the stria vascularis and glomerulus, respectively.³⁴ A variety of factors,

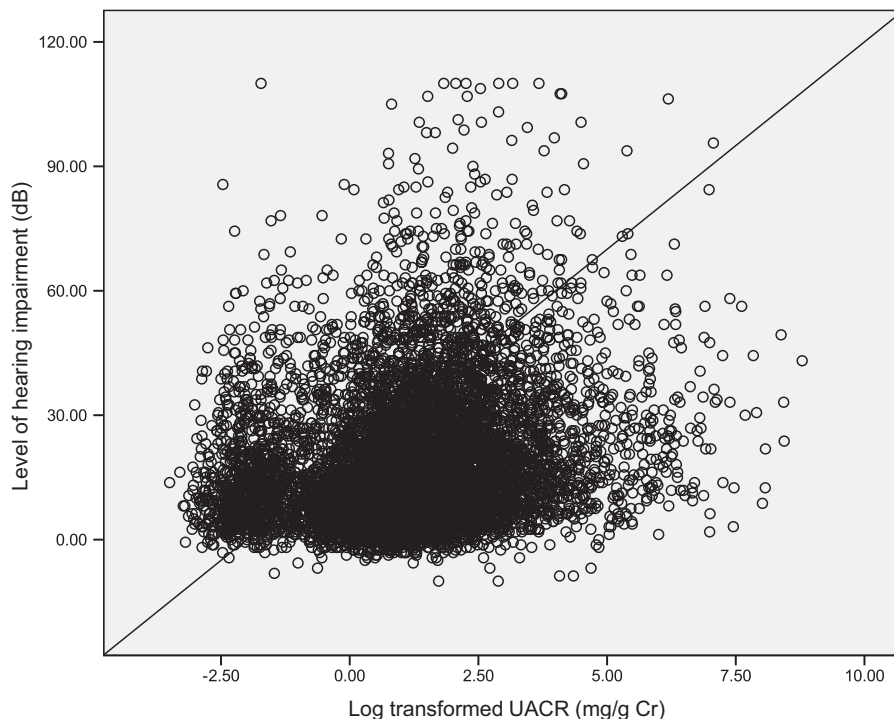


FIGURE 1. The relationship between the level of hearing impairment (decibels) and the log-transformed urinary albumin-to-creatinine ratio (UACR, mg/g Cr). Unweighted Spearman correlation tests were performed with age, sex, tobacco use, heavy alcohol use, educational background, occupational noise exposure, obesity, hypertension, diabetes, total serum cholesterol, and estimated glomerular filtration rate <60 mL/min/1.73 m² as covariates. (Spearman correlation, unadjusted $r=0.226$, adjusted $r=0.076$, $P<0.001$).

including electrolyte disturbances, proteinuria, and hypertension, appear to have cumulative effects on the degeneration of auditory function in patients with renal failure.³⁵ Although we adjusted for eGFR <60 mL/min/1.73 m², representing renal failure, we could not exclude the possibility of a residual relationship between albuminuria and decreased renal function.

The major strength of our study is the large, nationally representative sample of adult Koreans. To the best of our knowledge, this is the first study to demonstrate that albuminuria was positively associated with the severity of hearing impairments using nationally representative data.

Nevertheless, this study has some limitations. First, we could not take into account the use of angiotensin receptor blocker (ARB) or/and angiotensin-converting enzyme (ACE) inhibitor, which may reduce the degree of albuminuria. Second, we used a single urine spot sample to assess the UACR. Third, although we adjusted for many confounding factors, residual or hidden confounding variables cannot be excluded, similar to other cross-sectional studies. Finally, because Korea is a racially homogenous nation, future studies from other ethnicities, including western populations, are needed to strengthen the determination of the association between hearing impairment and albuminuria.

In summary, we found an association between moderate-to-profound hearing impairment and albuminuria in the Korean population aged 19 years or older. Additionally, the severity of hearing impairment was positively associated with increasing UACR. Although we could only speculate on the possible mechanisms for the association of hearing impairment and

albuminuria, we are the first to identify a relationship between 2 important public health problems. Because albuminuria is a modifiable risk factor, the current observation might lead to screening for albuminuria and therapeutic intervention with ARB or/and ACE inhibitor in the prevention of hearing impairment.

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