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Low-grade albuminuria is associated with hearing loss in non-diabetic US males

A cross-sectional analysis of 1999-2004 national health and nutrition examination survey

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Abstract

High levels of albuminuria have been demonstrated to associate with hearing loss in non-diabetic people, while the clinical impact of low-grade albuminuria has attracted less attention. This cross-sectional population-based study aimed to examine whether hearing loss in non-diabetic United States (US) adults is independently associated with low-grade albuminuria or reduced estimated glomeruli filtration rate (eGFR).

A total of 2518 participants aged 20 to 69 years were selected from the US National Health and Nutritional Examination Survey database. Participants with diabetes or high-grade albuminuria were excluded. Hearing loss was assessed using low-frequency pure-tone average (LFPTA) thresholds (0.5, 1.0, 2.0 kHz) and high-frequency pure-tone average (HFPTA) thresholds (3.0, 4.0, 6.0, 8.0 kHz). Logistic and linear regression analyses were used to evaluate associations between renal function indicators and hearing loss.

The median age of included participants was 37.4 years, and 55% of them were female. Multivariate analysis revealed that participants with urinary albumin-to-creatinine ratio (UACR) in the highest tertile had a significantly higher risk of hearing loss (OR, 1.79; 95% CI, 1.01–3.19) and higher HFPTA thresholds (β: 2.23; SE: 0.77). Participants with eGFR <60 mL/min/1.73 m^2 had higher LFPTA thresholds (β: 4.31; SE: 1.79). After stratification by sex, a significant risk remained only for males in the highest UACR tertile, with 2.18 times the risk of hearing loss (95% CI, 1.06–4.48).

Non-diabetic US males with low-grade albuminuria are at increased risk of hearing loss, independent of eGFR.

Abbreviations: BMI = body mass index, CDC = Centers for Disease Control and Prevention, CKD = chronic kidney disease, CSGLM = Complex Samples General Linear Model, CVD = cardiovascular disease, DPOAE = distortion-product otoacoustic emissions, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HFPTA = high-frequency pure-tone average, IHC = inner hair cells, KIM-1 = kidney injury molecule 1, LDL = low-density lipoprotein, LFPTA = low-frequency pure-tone average, MDRD = modification of diet in renal disease, MEC = mobile examination center, MET = metabolic equivalent of task, NCHS = National Center for Health Statistics, NHANES = National Health and Nutritional Examination Survey, OHC = outer hair cells, OR = odds ratio, PTA = pure-tone average, SD = standard deviation, TG = triglyceride, UACR = urinary albumin-to-creatinine ratio.

Keywords: albumin-to-creatinine ratio, diabetes, glomerular filtration rate, hearing loss, National Health and Nutritional Examination Survey (NHANES)

1. Introduction

Damage to the structural and functional integrity of the cochlea and the auditory nerve caused by aging, noise, ototoxicity, or chronic and acute diseases can result in various degrees of hearing impairments, ranging from hearing loss to elevation in pure-tone thresholds.[1] Noise-induced hearing loss often results from damage to the outer hair cells (OHC) or inner hair cells (IHC) in the organ of Corti; high-frequency hearing is more vulnerable to noise than low-frequency hearing.[2] Noise-induced hearing loss

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is also associated with damage to the afferent synapses at the base of the IHC resulting in degeneration of spiral ganglion neurons in the cochlea.[3] In addition, smoking,[4] diabetes,[5,6] and cardiovascular disease[7] have been suggested to be risk factors of hearing loss. Many risk factors have been linked to impaired cochlear blood flow, which is crucial for auditory function due to its extreme sensitivity to hypoxia.[8]

Hearing loss also is prevalent among patients with chronic kidney disease (CKD) without knowing the underlying mechanisms.[9–11] While the similar physiological, ultrastructural, and antigenic features between the kidney glomeruli and the stria vascularis of the cochlea may play a role in the above-mentioned relationship.[9] Interestingly, recent reports suggest that 2 of the key biochemical indicators of CKD, reduced glomerular filtration rate (GFR) and elevated urine albumin concentration, also are associated with hearing loss.[9,11,12]

GFR is the most commonly used indicator of kidney function; its decline is associated with numerous clinical conditions and correlates with decreases in excretory, endocrine, and metabolic functions.[13] Several studies have shown a correlation between decreased GFR and hearing loss, independent of diabetes and several cardiovascular factors known to affect hearing.[9,11,14] Albuminuria, the abnormal leakage of albumin into the urine, is caused by injury to glomerular capillaries and subsequent vessel damage and leakage.[15] As such, albuminuria is an indicator of generalized vascular dysfunction that may involve extrarenal complications linked to cardiovascular and metabolic disease.[16] Albuminuria has been suggested to be an independent risk factor for hearing loss in patients with or without diabetes.[11,12,17]

Several lines of evidence indicated the association between hearing loss and higher levels of albuminuria, defined by urine albumin/creatinine ratio (UACR) ≥ 30 mg/g.[12,17] In contrast, the clinical impact of low-grade albuminuria (UACR < 30 mg/g) has been rarely explored. Herein, we hypothesized that hearing loss might develop in non-diabetic people with low-grade albuminuria. To test this hypothesis, we evaluated the associations between hearing loss and 2 renal function indicators, UACR and estimated GFR (eGFR), in a large cohort of US non-diabetic adults.

2. Methods

2.1. Database

This cross-sectional study was a secondary analysis of data from the US National Health and Nutrition Examination Survey (NHANES) database sponsored by National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). The survey was designed to evaluate the health and nutritional status of adults and children in the USA. It used a complex, multistage sampling design to collect and analyze data representative of the national, non-institutionalized population of the USA.

All NHANES participants completed a household interview and took an extensive examination in a mobile examination center (MEC), including a physical examination, specialized measurements, and laboratory tests. The NHANES database was reliable and equated to a population-level assessment.[18] The NCHS Research Ethics Review Board reviewed and approved NHANES, and all survey participants provided written informed consent. Therefore, no further ethical approval and informed consent were required to perform the secondary analyses undertaken in this manuscript.

2.2. Study population

This population-based, cross-sectional study reviewed data from 3 cycles of NHANES during 1999 to 2004. These cycles were chosen because audiometric data were available. Included subjects were adults aged 20 to 69 years with complete audiometry data. Exclusion criteria included implanted grommets, abnormal otoscopy, impacted cerumen, collapsing ear canals, and other abnormalities in audiometry, abnormal tympanometry (defined by peak pressure ≤ -150 daPa or compliance ≤ 0.3 mL), and a difference > 10 dB between test and retest thresholds at 1 kHz. NHANES did not survey for congenital/genetic or sudden hearing loss; therefore, participants with low-frequency pure-tone average (LFPTA) or high-frequency pure-tone average (HFPTA) > 3 standard deviations (SD) above the mean for their age group or > 15 dB difference between ears on either LFPTA or HFPTA were excluded from further analysis in accordance with previous studies.[19]

Because this study evaluated the association between low-grade albuminuria and hearing loss in a non-diabetic population, participants with diabetes or micro- or macro-albuminuria (UACR: 30–300 mg/g and >300, respectively) were excluded. Diabetes was defined by a positive response to any of the following questions: "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"; "Are you now taking insulin?"; "Are you now taking diabetic pills to lower your blood sugar? These are sometimes called oral agents or oral hypoglycemic agents." or by HbA1c $\geq$7% or fasting glucose >125 mg/dL in laboratory measurements in accordance with WHO recommendations.[20]

2.3. Outcome measures

2.3.1. Audiometric measures. The audiological examination was performed in a MEC equipped with sound-isolated rooms. The examination consisted of an audiometric questionnaire, an otoscopic examination, tympanometry, and pure-tone air-conduction threshold measures at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz.[21]

Briefly, hearing threshold testing was conducted on both ears of examinees at 6 frequencies (0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz) using the modified Hughson–Westlake procedure and invoking the automated testing mode of the audiometer. After excluding individuals with abnormal otoscopic examinations in either ear, we computed the LFPTA at 0.5, 1.0, and 2.0 kHz and HFPTA at 3.0, 4.0, 6.0, and 8.0 kHz for each ear. In accordance with previous studies, participants with LFPTA or HFPTA >25 dB in either ear were classified as having hearing loss.[19,22] Hearing loss was assessed as the primary endpoint. We also assessed the LFPTA and HFPTA (dB) of the most impaired ear as the secondary endpoints.

Demographic data including age, sex, race/ethnicity, education level, family income-to-poverty ratio, and veteran/military status were obtained through in-person interviews conducted by trained interviewers. Collected data were weighted according to the NHANES protocol.

2.3.2. UACR. Urinary albumin and creatinine measures were obtained from the laboratory data in NHANES (https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/LAB18.htm). The UACR was calculated and categorized into 3 groups by tertiles: 0 to 33rd

percentile, 0 to 4.09 mg/g; 34th to 66th percentile, 4.10 to 6.61 mg/g; 67th to 100th percentile, >6.61 mg/g.

2.3.3. eGFR. The glomerular filtration rate was estimated from the serum creatinine concentration using the Modification of Diet in Renal Disease (MDRD) equation: eGFR = 175 × [(calibrated serum creatinine in mg/dL) – 1.154] × (age – 0.203) × (0.742 if female) × (1.210 if African-American). Participants were grouped according to eGFR < 60, 60 to 89, and ≥90 mL/min/1.73 m^2.

2.3.4. Laboratory measures. The levels of HbA1c (%), fasting glucose (mg/dL), total cholesterol (mg/dL), triglyceride (TG) (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), and low-density lipoprotein (LDL) cholesterol (mg/dL) were collected from blood samples as previously described (https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/LAB18.htm; https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/LAB13.htm).

2.3.5. Comorbidities. The body mass index (BMI) was obtained from the NHANES examination measurements. Obesity was defined according to standard BMI categories as BMI ≥30 kg/m^2. Central obesity (abdominal obesity) was defined as waist circumference >102 cm for males and >88 cm for females. Hypertension was defined as the self-reported response "yes" to the question "Were you told on 2 or more different visits that you had hypertension, also called high blood pressure?" or "Because of your (high blood pressure/hypertension), have you ever been told to take prescribed medicine?" or by an average systolic blood pressure ≥140 mmHg in 3 consecutive measurements or an average diastolic blood pressure ≥90 mmHg in 3 consecutive measurements. Hyperlipidemia was defined as the self-reported response "yes" to the question "To lower your blood cholesterol, have you ever been told by a doctor or other health professional to take prescribed medicine?" or as a total cholesterol >200 mg/dL. Cardiovascular disease (CVD) was defined as a history of coronary heart disease, angina pectoris, heart attack, stroke, or congestive heart failure as assessed by the question "Has a doctor or other health professional ever told you that you have (disease)?"

2.3.6. Noise exposure. Loud noise/music exposure during the 24 hours preceding the exam was defined as a response "yes" to the NHANES question "Have you been exposed to loud noise or listened to music with headphones in the past 24 hours?" Firearm noise exposure was defined as a response "yes" to the question "Outside of work, have you ever been exposed to firearms noise for an average of at least once a month for a year?" Recreational noise exposure was defined as a response "yes" to the question "Outside of work, have you ever been exposed to other types of loud noise, such as noise from power tools or loud music, for an average of at least once a month for a year? By loud noise I mean noise so loud that you had to speak in a raised voice to be heard." Occupational noise exposure was defined as a response "yes" to the question "Thinking of all the jobs you have ever had, have you ever been exposed to loud noise at work for at least 3 months? By loud noise I mean noise so loud that you had to speak in a raised voice to be heard?"

2.3.7. Other lifestyle factors. Smoking status was classified as non-smoker, former smoker, or current smoker as follows: lifetime smoking of less than 100 cigarettes, non-smoker; lifetime smoking >100 cigarettes but not currently a smoker, former smoker; lifetime smoking >100 cigarettes and responded "yes" to the question "Do you smoke now?", current smoker. Alcohol consumption was classified as non-heavy drinker and heavy drinker, as follows: heavy drinker, consuming alcohol ≥ 4 times/wk in response to the question "In the past 12 months, how often did you drink any type of alcoholic beverage?" To estimate physical activity, we summed the product of weekly time spent in each activity reported by the participant multiplied by the metabolic equivalent of task (MET) value for that activity, yielding an MET-h index. One MET was defined as the energy cost of sitting quietly and was equivalent to a caloric consumption of 1 kcal/kg/h.[23–25]

2.4. Statistical analysis

Continuous variables were presented as the median and interquartile range, as determined using the Complex Samples General Linear Model (CSGLM). Categorical variables were presented as number and weighted percentages, as determined by the Chi-Squared test. Univariate and multivariate regression analyses were performed to examine the association between UACR or eGFR and hearing loss. Significant variables revealed in univariate analyses were then used to establish the final multivariable models. The regression models were additionally stratified by sex. All analyses included special sample weights, stratum, and primary sampling units (PSU) per recommendations by the NCHS. The post hoc power of the present study was over 90% in linear regression, as calculated by G*Power software. Analyses were two-sided, with $P < .05$ considered significant. All statistical analyses were performed using SAS version 9.4 (Windows NT version, SAS Institute, Inc., Cary, NC).

3. Results

3.1. Descriptive statistics

A total of 31,126 participants meeting the inclusion criteria were identified in the NHANES database (1999–2004), of whom 12,056 were aged 20 to 69. As shown in Figure 1, 9538 participants who met the exclusion criteria were excluded. As a result, the remaining 2518 participants comprised the study population of the present study. Using NHANES 3-year subsample weights, the sample size was equivalent to a population-based sample size of 87,289,806 participants.

Demographic and clinical characteristics of the study population are shown in Table 1. The median age was 37.4 years. The majority of the study population was female, non-Hispanic white, not poor, educated at or above high school level, without veteran/military status, without comorbidities, without noise exposure, non-smoker, and non-heavy drinker. Participants with and without hearing loss differed significantly with respect to age, sex, race, education level, veteran/military status, HbA1c, fasting glucose, total cholesterol, TG, HDL-cholesterol, LDL-cholesterol, central obesity, hypertension, hyperlipidemia, CVD history, firearm noise exposure, occupational noise exposure, smoking, alcohol consumption, and eGFR (all $P < .05$) (Table 1).

3.2. Associations between hearing loss and renal function indicators

Logistic regression analyses were applied to evaluate associations between hearing loss and renal function indicators (Table 2). After adjusting for significant variables identified in univariate

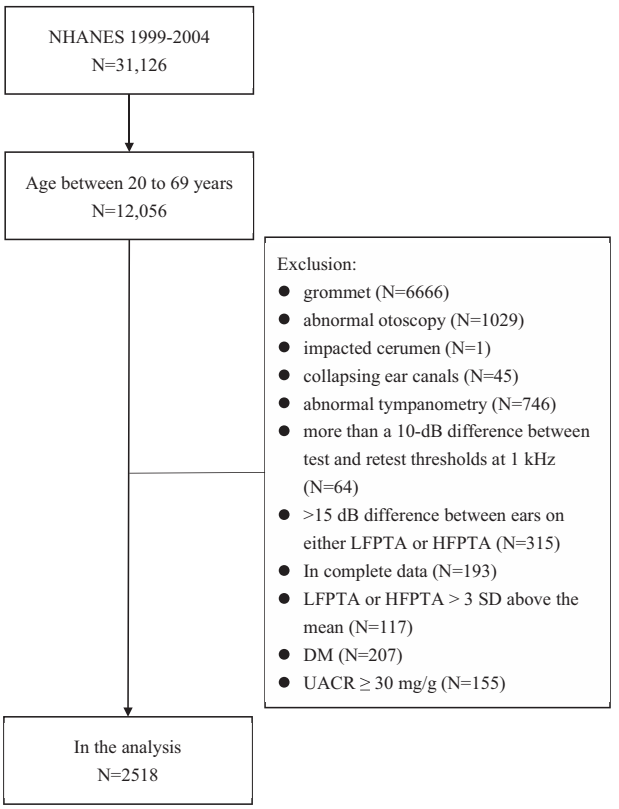

Figure 1. Flow chart of study population selection.

analyses, including age, sex, race, education level, veteran/military status, HbA1c, fasting glucose, hypertension, hyperlipidemia, CVD, firearm noise, occupational noise, smoking, alcohol consumption, and eGFR, multivariate analysis revealed that participants with UACR in the highest tertile (≥6.61 mg/g) had a greater risk of hearing loss (OR, 1.79; 95% CI, 1.01–3.19) compared with those with UACR in the first tertile (<4.09 mg/g). Stratified by sex, the result showed that the increased UACR was associated with the elevated risk of hearing loss in men (OR, 1.06; 95% CI, 1.00–1.12). Males with UACR ≥6.61 mg/g had a doubled risk of hearing loss (OR, 2.18; 95% CI, 1.06–4.48) than the reference group (Table 2).

3.3. Associations between hearing thresholds and renal function indicators

Linear regression analyses were applied to evaluate associations between hearing thresholds and renal function indicators (Table 3). After adjustment for significant variables identified in univariate analyses, including age, education level, HbA1c, fasting glucose, obesity, hypertension, hyperlipidemia, CVD, occupational noise, smoking, and eGFR, multivariate analyses revealed that participants with the lowest level of eGFR (<60 mL/min/1.73 m^2) had increased LFPTA ($\beta \pm SE = 4.31 \pm 1.79$, $P = .02$) compared with those with the highest level of eGFR (≥90 mL/min/1.73 m^2). This association was also observed in female participants when stratifying by sex ($\beta \pm SE = 4.26 \pm 1.79$, $P = .02$).

The higher UACR was significantly associated with slightly increased HFPTA ($\beta \pm SE = 0.15 \pm 0.07$, $P = .03$). Also, participants with the highest tertile of UACR (≥6.61 mg/g) had slightly greater HFPTA ($\beta \pm SE = 2.23 \pm 0.77$, $P = .01$) than those with the

Table 1

Demographic and clinical characteristics of the study population.

	All participants (n = 2518)	Without hearing loss (n = 2023)	With hearing loss (n = 486)	*P* value
Demographics				
Age, yr	37.37 (28.66–46.39)	34.69 (26.93–43.47)	50.54 (41.55–58.65)	<.001*
Sex				
Male	1084 (44.89%)	787 (40.61%)	297 (63.51%)	<.001*
Female	1434 (55.11%)	1245 (59.39%)	189 (36.49%)	
Race				
Mexican American	576 (8.26%)	470 (8.84%)	106 (5.74%)	<.001*
Other Hispanic	144 (7.13%)	122 (7.60%)	22 (5.11%)	
Non-Hispanic White	1251 (70.78%)	981 (68.84%)	270 (79.20%)	
Non-Hispanic African-American	470 (10.43%)	399 (11.28%)	71 (6.77%)	
Other, including multi-racial	77 (3.39%)	60 (3.44%)	17 (3.19%)	
Poverty income ratio*				
Not poor	1913 (80.85%)	1536 (80.48%)	377 (82.44%)	.41
Poor	400 (11.96%)	336 (12.38%)	64 (10.17%)	
Missing	205 (7.19%)	160 (7.14%)	45 (7.39%)	
Education level				
High school or above	1904 (84.67%)	1572 (85.54%)	332 (80.89%)	.02*
Never attended high school	614 (15.33%)	460 (14.46%)	154 (19.11%)	
Veteran/military status				
Yes	215 (9.35%)	138 (7.95%)	77 (15.46%)	<.001*
No	2303 (90.65%)	1894 (92.05%)	409 (84.54%)	
Laboratory				
HbA1c, %	5.14 (4.94–5.36)	5.12 (4.93–5.32)	5.26 (5.07–5.49)	<.001*
Fasting glucose, mg/dL	93.03 (87.43–99.30)	92.25 (87.12–98.67)	96.07 (89.99–102.31)	.002*
Total cholesterol, mg/dL	193.94 (170.83–220.35)	190.99 (167.82–217.49)	205.07 (187.06–234.08)	<.001*

(*continued*)

Table 1

(continued).

	All participants (n = 2518)	Without hearing loss (n = 2023)	With hearing loss (n = 486)	*P* value
TG, mg/dL	101.47 (68.64–148.96)	97.55 (67.07–143.92)	123.68 (84.16–186.97)	<.001*
HDL-cholesterol, mg/dL	50.19 (41.25–61.75)	50.84 (41.97–62.19)	47.33 (39.00–59.27)	.01*
LDL-cholesterol, mg/dL	116.02 (94.49–139.29)	113.60 (41.97–93.05)	127.15 (108.01–153.13)	<.001*
Comorbidities				
Obesity†				
No	1769 (72.08%)	1430 (72.69%)	339 (69.42%)	.23
Yes	749 (27.92%)	602 (27.31%)	147 (30.58%)	
Central obesity				
No	1319 (55.43%)	1086 (57.82%)	233 (45.07%)	<.001*
Yes	1199 (44.57%)	946 (42.18%)	253 (54.93%)	
Hypertension				
No	1959 (78.89%)	1680 (82.9%)	279 (61.48%)	<.001*
Yes	559 (21.11%)	352 (17.1%)	207 (38.52%)	
Hyperlipidemia				
No	1302 (54.11%)	1117 (58.07%)	185 (36.92%)	<.001*
Yes	1216 (45.89%)	915 (41.93%)	301 (63.08%)	
CVD history				
No	2430 (96.46%)	1984 (97.37%)	446 (92.53%)	<.001*
Yes	88 (3.54%)	48 (2.63%)	40 (7.47%)	
Noise exposure				
Loud noise/music in past 24 h				
No	2307 (91.57%)	1852 (90.97%)	455 (94.2%)	.08
Yes	211 (8.43%)	180 (9.03%)	31 (5.80%)	
Firearm noise				
No	2375 (93.16%)	1924 (93.79%)	451 (90.43%)	.003*
Yes	143 (6.84%)	108 (6.21%)	35 (9.57%)	
Recreational noise				
No	1915 (73.5%)	1530 (72.97%)	385 (75.8%)	.35
Yes	603 (26.5%)	502 (27.03%)	101 (24.2%)	
Occupational noise				
No	1950 (75.36%)	1589 (76.34%)	361 (71.11%)	.03*
Yes	568 (24.64%)	443 (23.66%)	125 (28.89%)	
Lifestyle				
Smoking				
Non-smoker	1410 (53.55%)	1191 (55.80%)	219 (43.77%)	<.001*
Former smoker	522 (21.68%)	374 (19.33%)	148 (31.90%)	
Current smoker	586 (24.77%)	467 (24.87%)	119 (24.34%)	
Heavy drinker				
No	2304 (90.52%)	1893 (91.77%)	411 (85.09%)	<.001*
Yes	214 (9.48%)	139 (8.23%)	75 (14.91%)	
Physical activity MET score	958.40 (383.67–2165.36)	983.44 (359.70–2249.15)	803.26 (447.91–1639.31)	.08
UACR‡, mg/g	5 (3.65–7.94)	4.95 (3.62–7.81)	5.39 (3.80–8.46)	.16
Percentile, n, (%)				
0–33rd (0–4.08 mg/g)	770 (33.22%)	636 (34.12%)	134 (29.30%)	.05
34–66th (4.09–6.60 mg/g)	832 (33.44%)	674 (33.86%)	158 (31.63%)	
67–100th (≥6.61 mg/g)	916 (33.34%)	722 (32.02%)	194 (39.07%)	
eGFR, mL/min/1.73 m^2	93.46 (80.8–111.71)	96.01 (83.16–115.09)	85.13 (75.01–100.97)	<.001*
≥90	1615 (57.93%)	1392 (62.17%)	223 (39.50%)	<.001*
60–89	877 (41.04%)	631 (37.40%)	246 (56.87%)	
<60	26 (1.03%)	9 (0.43%)	17 (3.63%)	
Outcome				
LFPTA of worse ear, dB	8.29 (4.99–12.91)	7.31 (4.38–11.06)	14.37 (9.50–19.74)	<.001*
HFPTA of worse ear, dB	13.85 (9.02–21.30)	11.92 (7.96–16.35)	33.22 (28.13–41.19)	<.001*

Continuous variables are presented as the median and interquartile range, as determined by Complex Samples General Linear Model (CSGLM). Categorical variables are presented as counts (weighted percentage), as determined by Chi-Squared test.

CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HFPTA = high-frequency pure-tone average, LDL = low-density lipoprotein, LFPTA = low-frequency pure-tone average, TG = triglyceride, UACR = urine albumin–creatinine ratio.

* Poverty income ratio: >1, not poor; ≤1, poor.

† Obesity was defined as BMI ≥ 30 kg/m^2.

‡ UACR was categorized into 3 groups by tertiles: 0–33rd percentile, 0–4.08 mg/g; 34–66th percentile, 4.09–6.60 mg/g; 67–100th percentile, ≥6.61 mg/g.

Table 2

Multivariate logistic regression analyses of associations between hearing loss and renal function indicators.

	Total population aOR (95% CI)	Males aOR (95% CI)	Females aOR (95% CI)
UACR*, mg/g	1.04 (0.98–1.10)	**1.06 (1.00–1.12)**	1.03 (0.94–1.12)
Percentile			
0–33rd (0–4.08 mg/g)	Reference	Reference	Reference
34–66th (4.09–6.60 mg/g)	1.39 (0.69–2.77)	1.74 (0.70–4.33)	1.15 (0.60–2.2)
67–100th (≥6.61 mg/g)	**1.79 (1.01–3.19)**	**2.18 (1.06–4.48)**	1.37 (0.54–3.47)
eGFR	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.99 (0.98–1.01)
≥90	Reference	Reference	Reference
60–89	0.92 (0.56–1.51)	1.00 (0.52–1.92)	0.80 (0.37–1.74)
<60	2.89 (0.42–19.91)	3.40 (0.65–17.93)	4.00 (0.31–51.39)

Significant values are in bold ($P < .05$).

Multivariate analyses are adjusted for age, sex, race, education level, veteran/military status, HbA1c, fasting glucose, hypertension, hyperlipidemia, CVD, firearm noise, occupational noise, smoking, alcohol consumption, and eGFR.

aOR = adjusted odds ratio, CI = confidence interval, eGFR = estimated glomerular filtration rate, HFPTA = high-frequency pure-tone average, LFPTA = low-frequency pure-tone average, OR = odds ratio, UACR = urine albumin creatinine ratio.

* UACR was categorized into 3 groups by tertiles: 0–33rd percentile, 0–4.08 mg/g; 34–66th percentile, 4.09–6.60 mg/g; 67–100th percentile, ≥6.61 mg/g.

lowest tertile of UACR (<4.09 mg/g) after adjustment for age, sex, race, education level, veteran/military status, HbA1c, fasting glucose, total cholesterol, obesity, hypertension, hyperlipidemia, CVD, loud noise/music in last 24 hours, firearm noise, occupational noise, smoking, alcohol consumption, and eGFR. The similar results were observed in female participants (β±SE = 2.25 ± 1.03, $P = .03$) (Table 3).

4. Discussion

This population-based cross-sectional study found that among non-diabetic participants with UACR < 30 mg/g, participants with UACR ≥6.61 mg/g had a significantly higher risk of hearing loss than those with UACR <4.09 mg/g after adjusting for eGFR. With sex-stratified analysis, a significant risk of hearing loss remained for males in the highest UACR tertile, but not identified for females. Thus, non-diabetic males with low-grade albuminuria are at increased risk of hearing loss, independent of eGFR. In addition, we found that the increased UACR was significantly associated with slightly elevated HFPTA, whereas participants with UACR ≥6.61 mg/g had slightly elevated HFPTA than those with UACR <4.09 mg/g but was observed only in females by sex-stratified analysis.

A large-cohort study by Kang et al revealed that in non-diabetic participants, there was a significant correlation between UACR and elevated average hearing threshold, and participants in the highest tertile of low-grade albuminuria were at significant higher risk of hearing loss.[11] However, in contrast to our findings, the associations were observed in both males and females.[11] Furthermore, Kim et al found a significant correlation between UACR and elevated pure-tone average at 3 and 6 kHz in males and at 1, 3, 4, and 6 kHz in females.[26] And a significant higher risk of hearing loss was observed in females with UACR ≥ 30 mg/g.[26] The gender discrepancy between the above 2 studies and the current study may be in part due to the ethnic makeup of cohorts used between studies, Korean cohorts in the studies of Kang et al[11] and Kim et al,[26] and the diverse ethnic background of the US population used in the present study. Notably, ethnic

Table 3

Multivariate linear regression analyses of associations between hearing thresholds and renal function indicators.

	LFPTA†			HFPTA‡		
	Total β ± SE	Males β ± SE	Females β ± SE	Total β ± SE	Males β ± SE	Females β ± SE
UACR*, mg/g	0.04 ± 0.04	0.03 ± 0.06	0.05 ± 0.06	**0.15 ± 0.07**	0.35 ± 9.08	0.11 ± 0.08
Percentile						
0–33rd (0–4.08 mg/g)	Reference	Reference	Reference	Reference	Reference	Reference
34–66th (4.09–6.60 mg/g)	−0.15 ± 0.50	−0.15 ± 0.73	−0.05 ± 0.62	0.81 ± 0.71	0.67 ± 1.19	0.95 ± 0.85
67–100th (≥6.61 mg/g)	0.99 ± 0.50	1.02 ± 0.69	0.96 ± 0.90	**2.23 ± 0.77**	2.17 ± 1.17	**2.25 ± 1.03**
eGFR, mL/min/1.73 m^2	−0.002 ± 0.02	−0.02 ± 0.02	0.003 ± 0.01	0.01 ± 0.01	−0.01 ± 0.02	0.01 ± 0.01
≥90	Reference	Reference	Reference	Reference	Reference	Reference
60–89	0.01 ± 0.56	−0.23 ± 0.60	0.23 ± 0.76	−0.60 ± 0.78	0.65 ± 0.91	−1.37 ± 1.05
<60	**4.31 ± 1.79**	NA	**4.26 ± 1.79**	4.40 ± 3.99	NA	6.56 ± 4.02

Significant values are in bold ($P < .05$).

β = beta coefficient, eGFR = estimated glomerular filtration rate, HFPTA = high-frequency pure-tone average, LFPTA = low-frequency pure-tone average, SE = standard error, UACR = urine albumin creatinine ratio.

* UACR was categorized into 3 groups by tertiles: 0–33rd percentile, 0–4.08 mg/g; 34–66th percentile, 4.09–6.60 mg/g; 67–100th percentile, ≥6.61 mg/g.

† Multivariate analyses are adjusted for age, education level, HbA1c, fasting glucose, obesity, hypertension, hyperlipidemia, CVD, occupational noise, smoking, and eGFR.

‡ Multivariate analyses are adjusted for significant baseline characteristics including age, sex, race, education level, veteran/military status, HbA1c, fasting glucose, total cholesterol, obesity, hypertension, hyperlipidemia, CVD, loud noise/music in last 24 hours, firearm noise, occupational noise, smoking, alcohol consumption, and eGFR.

differences in the association between albuminuria and cardiovascular and kidney disease have been reported,[27] supporting the cohort ethnicity theory.

Another difference between previous studies and the current study is the definition of albuminuria for people with UACR < 30 mg/g. Microalbuminuria is defined as UACR of 30–300 mg/g, and macroalbuminuria (or proteinuria) is defined as a UACR ≥ 300 mg/g.[28] And the present study investigated low-grade albuminuria that is defined as UACR < 30 mg/g, below threshold of microalbuminuria. The same definition of low-grade albuminuria has been reported previously.[11,16] However, Jung et al considered UACR < 30 mg/g as "without albuminuria"[17]; therefore, their control group of patients "without" albuminuria included subjects equivalent to those in our low-grade albuminuria group. In addition, Cherney et al[29] considered UACR < 30 mg/g as normoalbuminuria. Given that UACR < 30 mg/g has been demonstrated to be associated with hearing loss, periodontitis, CVD, and memory impairment in specific populations,[11,16,30,31] investigation of UACR < 30 mg/g has clinical significance regardless of the designation used by distinct studies.

No significant association between reduced eGFR and risk of hearing loss was observed in the present study, whereas eGFR < 60 mL/min/1.73 m^2 was correlated with slightly elevated LFPTA than those with eGFR ≥ 90 mL/min/1.73 m^2 in females. Several studies have shown a significant negative correlation between eGFR and hearing loss in cohorts of non-diabetic[9,11] and diabetic [14] participants, and both reduced eGFR and elevated UACR correlate with the severity of hearing impairment.[14]

The anatomic and physiological similarity between cochlear and renal microcirculation[9,32] may underlie the above-mentioned observations.[9,11,14] Similar to renal microcirculation in the glomerulus, cochlear microcirculation also possesses selective transportation mechanisms to maintain ion concentration gradients between blood, perilymph, and endolymph.[32–34] Damage to the stria vascularis may be associated with an abnormal vasomotor reactivity that was commonly observed in nephropathy patients,[35] and vasomotor defects have been suggested to be at least in part responsible for neurosensorial hypoacusia in chronic nephropathy.[32] Furthermore, a mouse cDNA microarray analysis found similar gene expression profiles between the cochlea and kidney, suggesting common pathophysiologic mechanisms shared by these 2 organs.[36] For example, kidney injury molecule 1 (KIM-1) was found to be expressed in the rat cochlea, as a novel cochlear injury molecule.[37] And the common biochemical characteristics shared by the ear and kidney have been proposed as potential pharmaceutical targets for specific diseases.[38]

The strength of this cross-sectional study is that NHANES provides comprehensive and nationally representative data drawn from a large and diverse sample of US participants. Therefore, the current findings are likely generalizable to the overall US population. In addition, hearing loss in the present study was objectively measured by audiometry and defined by standard criteria. We included UACR and GFR as both continuous and categorical variables. On the other hand, several factors limit the applicability of these findings. First, due to the cross-sectional nature of the NHANES dataset, causal inferences cannot be made and the onset and progression of hearing loss cannot be determined. Furthermore, inaccurate reporting or recall bias may have occurred because NHANES surveys are based on individual interviews and questionnaires. Information on the use of ototoxic drugs was not included in our analysis because of the lack of the relevant information in the NHANES database. Further longitudinal studies are highly warranted to confirm our findings and to investigate the mechanisms underlying the current findings.

5. Conclusion

Low-grade albuminuria is independently associated with a greater risk of hearing loss in US non-diabetic adult males. Low-grade albuminuria might be of clinical importance and may be monitored by clinicians for the health of hearing.

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