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Association between dipstick proteinuria and hearing impairment in health check-ups among Japanese workers: a cross-sectional study

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Abstract

Objective: Prevention of hearing impairment is important because it is difficult to recover from it. Epidemiological studies have examined the risk factors for hearing impairment; however, the association between dipstick proteinuria and hearing impairment has not been previously examined. This study aimed to clarify the association between dipstick proteinuria and the prevalence of hearing impairment.

Design: Cross-sectional study**.**

Setting: Office workers and factories workers all over Japan.

Participants: The total number of subjects was 7,005, all of whom were employees of the same company. Of these, we recruited 6,192 subjects who underwent hearing test by audiometry in health checkups (mean age 44.9 years, men 88.3%).

Primary Outcomes: Hearing test was performed by using audiometry at two frequencies (1 kHz, 4 kHz) during an annual health checkup prescribed by law in Japan. We defined inability of subjects to respond to 30 dB at 1 kHz and/or 40 dB at 4 kHz as total moderate hearing impairment. In addition, we defined moderate hearing impairment at 1 kHz (4 kHz) as an abnormal finding at 1 kHz (4 kHz).

Results: 324 (5.2%) subjects had total moderate hearing impairment, including 107 (1.7%) with moderate hearing impairment at 1 kHz and 278 subjects (4.5%) with moderate hearing impairment at 4 kHz. Dipstick proteinuria was positively associated with the prevalence of total moderate hearing impairment, as well as moderate hearing impairment at both 1 kHz and 4 kHz. The prevalence of total moderate hearing impairment among subjects with proteinuria ≥2+ was 22.9%, while that among subjects who did not have proteinuria was 5.2% (*P* for difference <0.01).

Conclusions: Dipstick proteinuria was positively associated with prevalence of

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moderate hearing impairment in Japanese workers. Our results suggest that medical examination including urine test is effective in detecting hearing impairment.

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Strength and limitations of this study

- Little has been reported on the association between dipstick proteinuria which is one of findings that microvessels are damaged and hearing impairment.
- Study participants of this study consisted of both healthy workers and unhealthy workers, because this study was based on annual health check-up in a company according to Japanese law.
- Our research were unable to use precise information on hearing tests compared with hearing tests in hospital because hearing tests in health check-up was consisted of tests in 1 kHz and 4 kHz..

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Introduction

Hearing impairment (HI) is a common symptom among older people. According to the World Health Organization (WHO) fact sheet published in February 2017, almost one-third of older people aged 65 years or over have HI. Prevention of HI is important in public health not only because HI is a condition that makes communication uncomfortable, but also because it is associated with a risk of dementia (1-3). A recent review reported that hearing loss in midlife (45–65 years old) was also associated with a risk of dementia (4). Dementia is an important health problem in industrial countries today and is anticipated to become an important health problem worldwide in the future. A trial estimated that the number of subjects suffering dementia might reach 80 million by 2040 (5).

It is difficult to recover from HI. Therefore, several epidemiological studies aimed at finding risk factors for HI have been carried out. They found many risk factors such as aging, exposure to loud noises, and medications. Of these, associations with lifestyle-related diseases concerned with microvascular disorders were examined in many studies. A meta-analysis of 13 cross-sectional studies suggested that a higher prevalence of HI was observed in diabetic patients compared with in non-diabetic patients (6). For hypertension, a study in a Korean population showed a positive association between hypertension and the risk of HI (7). In a similar study conducted among Hispanics/Latinos in United States, not such association was found (8). Recently, a cross-sectional study of Korean subjects showed that albuminuria, low-grade albuminuria, urine albumin creatinine ratio, and eGFR were associated with HI among non-diabetic subjects (9-11). However, the association between dipstick proteinuria, which is a test commonly administered in health-checks, and HI has not been examined

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yet.

Therefore, we aimed to examine the association between dipstick proteinuria and prevalence of HI. If dipstick proteinuria is associated with HI, the dipstick urine test would be beneficial in detecting individuals at a high risk of HI. We hypothesize that the degree of dipstick proteinuria is positively associated with prevalence of HI. To test our hypothesis, we conducted a cross-sectional study among Japanese workers.

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Method

Subjects

The subjects were 19-to-66-year-old employees of Japan Tobacco Inc. (JT). They worked offices and factories all over Japan. There were 7,005 subjects in total (6,039 men and 966 women). They underwent annual health check-ups between 2008 and 2016. In subjects who had undergone annual health check-ups twice or more, we used the latest data for the analyses. We excluded 813 subjects from the analysis who did not undergo hearing test by audiometry. Therefore, we used data from 6,192 subjects (5,466 men and 726 women) in the analyses.

We used anonymized data with the permission of JT. The study was approved by the Ethics Committee of Dokkyo Medical University (Univ-28018).

Risk factor survey

The annual health check-up was conducted as required by the Industrial Safety and Health Act under Japanese law. The check-up consisted of a body weight measurement with light clothing, ascertaining medical history, alcohol consumption/smoking status, a hearing test, a vision test, blood pressure measurement, blood tests, and dipstick urine tests. The hearing test was performed using audiometry. In accordance with Japanese law, two categories of hearing tests were applied at 1 kHz and 4 kHz for each ear. Inability to respond to 30 dB at 1 kHz and/or 40 dB at 4 kHz was defined as the threshold for "abnormal." We defined as moderate hearing impairment (moderate HI), if there was an abnormal finding in any one category. Likewise, we defined moderate HI at 1 kHz (4 kHz) as there was an abnormal finding at 1 kHz (4 kHz). Blood pressure was measured using automated sphygmomanometers. eGFR was calculated using the

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following formula established by the working group of the Japanese Chronic Kidney Disease Initiative: eGFR (mL/min/1.73m^2) = 1.94 × (serum creatinine)−1.094 × (age)−0.287 × 0.739 (if female) (12). For HbA1c, the National Glycohemoglobin Standardization Program [NGSP] value was mainly used. For 25 subjects, only the Japan Diabetes Society [JDS] value was available, and therefore we adapted their value to the NGSP value using the conversion formula as follows; HbA1c (NGSP) = 1.02 × HbA1c (JDS) + 0.25% (13).

Statistical analysis

Age, sex, and age- and sex- adjusted means or proportions of cardiovascular risk factors such as body mass index (BMI), waist circumference, systolic and diastolic blood pressure, medication for hypertension, serum lipids, medication for hypercholesterolemia, HbA1c level, medication for diabetes mellitus, serum creatinine level, hepatic enzymes, hemoglobin level, proportion of current smokers, dipstick urine test for proteinuria and urine glucose, and history of working in a noisy place between 2008–2016 (noisy work environment) were calculated according to the presence of moderate HI. We also calculated the characteristics of subjects according to degree of proteinuria (-, +-, + and ≥2+). We calculated age and sex-adjusted prevalence of HI according to presence of proteinuria (-, +-, + and ≥2+), diabetes mellitus (yes or no), hypertension (yes or no), urinary glucose (-, +-, + and ≥2+) and serum creatinine level (sex-specific quintile). We defined hypertension as ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure and/or taking medication for hypertension, and defined diabetes mellitus as ≥6.5% HbA1c and/or taking medication for diabetes mellitus. For proteinuria and diabetes mellitus, we calculated multivariable adjusted

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prevalence of moderate HI according to the categories described above. We used confounding variables for adjustment that included age, sex, BMI, hypertension, diabetes mellitus, serum creatinine and noisy work environment for calculation of proteinuria, and include age, sex, BMI, hypertension, serum creatinine, proteinuria and noisy work environment for calculation of diabetes mellitus. In addition to the associations between these risk factors and moderate HI, we examined the association between Chronic Kidney Disease (CKD) and prevalence of moderate HI. We defined CKD as eGFR <60 (mL/min/1.73m^2) and/or proteinuria 2+ or more. We tested for sex interaction in each analysis and found no significant interactions.

We used SAS version 9.4 software (SAS Institute, Cary, NC) for all analyses. We used analysis of variance and analysis of covariance. We excluded subjects from analysis if subjects had any missing. *P* values <0.05 were regarded as statistically significant and *P* values between 0.05 and 0.10 were regarded as borderline significant.

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Results

In the present study, among 6,192 subjects, 324 subjects (5.2%) had moderate HI, including 107 subjects (1.7%) with moderate HI at 1 kHz, 278 subjects (4.5%) with moderate HI at 4 kHz, 218 subjects (3.5%) with moderate HI in one ear and 106 subjects (1.7%) with moderate HI in two ears.

Table 1 shows the characteristics of subjects according to the presence of moderate HI. Compared with subjects who did not have moderate HI, subjects with moderate HI showed significantly higher age, HbA1c level, proportion receiving medication for diabetes mellitus, serum creatinine level, aspartate transaminase (AST) level, gamma-glutamyl transpeptidase (gamma-GT) level and proportion of dipstick proteinuria, while systolic blood pressure and proportion of dipstick urine glucose with borderline significance,.

Table 2 shows the characteristics of subjects according to the degree of proteinuria. Compared with subjects who did not have proteinuria, subjects with proteinuria of 2+ or more showed higher age, BMI, waist circumstance, blood pressure, triglyceride level, HbA1c level, hepatic enzyme levels, proportion of dipstick urine glucose, and proportion receiving medication for hypertension, hypercholesterolemia and diabetes mellitus; while they showed lower HDL-cholesterol level and hemoglobin levels.

Table 3 shows the prevalence of moderate HI according to the degree of cardiovascular risk factors. Proteinuria was positively associated with the prevalence of moderate HI and its subtypes. The prevalence of total prevalence of moderate HI among subjects with proteinuria of 2+ or more was 22.9%, while that among subjects who did not have proteinuria was 5.2% (*P* for difference <0.01). The prevalence of moderate HI at 1 kHz and 4 kHz among subjects with proteinuria of 2+ or more was 8.0% and 20.5%,

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respectively, while those among subjects who did not have proteinuria was 1.7% and 4.4% (*P* for difference were 0.03 and <0.01). Subjects with diabetes mellitus showed higher prevalence of moderate HI, compared with subjects who without diabetes mellitus (7.8% vs. 5.1%; *P* for difference =0.03), however, this association was not clear in moderate HI at 1 kHz or 4 kHz. No associations were found between moderate HI and its subtypes with hypertension, urinary glucose and serum creatinine level.

We also examined the association between moderate HI according to its subtypes and CKD. Presence of CKD was significantly associated with the prevalence of total prevalence of moderate HI and moderate HI at 4 kHz. After adjustment for age, sex, BMI, hypertension, diabetes mellitus and noisy work environment, the total prevalence of moderate HI among subjects with CKD was 8.9%, whereas it was 5.0% among subjects without CKD (*P* for difference <0.01). The prevalence of moderate HI at 4 kHz was 8.1% among subjects with CKD, and it was 4.3% among subjects who without CKD (P for difference <0.01).

For hemoglobin, AST and gamma-GT, we examined the associations with prevalence of moderate HI according to their sex-specific quintiles, and failed to find any significant associations among those factors.

Table 4 shows associations between prevalence of total moderate HI and proteinuria and diabetes mellitus according to the number of ears with HI. Proteinuria was positively associated with total prevalence of moderate HI in one ear, but not in two ears, while diabetes mellitus was positively associated with total prevalence of moderate HI in two ears.

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Discussion

In the present study, we found that subjects with dipstick proteinuria of 2+ or more showed significantly higher prevalence of HI in all ranges, at 1 kHz and 4 kHz, compared with subjects without dipstick proteinuria. Subjects with diabetes mellitus or CKD also showed a higher prevalence of HI compared with subjects without diabetes mellitus or CKD.

A previous study on Korean subjects showed a positive association between albuminuria and prevalence of total HI (11). In this study, degree of albuminuria was significantly associated with moderate to severe HI defined as a hearing threshold level for the superior ear of ≥40 dB, both in low/mid (0.5, 1.0, and 2.0 kHz) and high (3.0, 4.0, and 6.0 kHz) frequencies. However, the association between degree of HI and mild HI defined as a hearing threshold level for the superior ear of 26-40 dB was not significant. Subjects with albuminuria had 1.5-fold higher prevalence of moderate to severe HI in all frequency ranges 1.7-fold higher at low/mid frequency and 1.3-fold higher at high frequency (11). Similarly, the present study revealed similar associations between dipstick proteinuria level and HI. We recalculated to examine the association between dipstick proteinuria of 1+ or more and the prevalence of HI, and found that dipstick proteinuria of 1+ or more was also significantly associated with moderate HI and moderate HI at 4 kHz, but not moderate HI at 1 kHz (data not shown). For diabetes mellitus, a meta-analysis showed that HI in subjects with diabetes mellitus was 2.1-fold more prevalent than in subjects without diabetes mellitus (6). In the present study, subjects with diabetes mellitus showed a 1.5-fold higher prevalence of moderate HI compared with subjects without diabetes mellitus. With regard to hypertension, a previous study of the Framingham cohort showed that hypertension in older people was

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positively associated with HI (14). In this study, age-adjusted high-frequency hearing ability of hypertensive men was significantly lower than that of non-hypertensive men, and age-adjusted low-frequency hearing ability of hypertensive women was significantly lower than that of non-hypertensive women. Recently, a study of Korean men and women showed a positive association between hypertension and HI (7), whereas a study in Hispanic/Latina men and women failed to find such an association (8). In the present study, borderline significant association between hypertension and total HI was found in men or in women. With regard to CKD, a study in Koreans reported that lower eGFR as eGFR < 60 (mL/min/1.73m^2) was positively associated with 1.6-fold higher prevalence of moderate to severe HI at both low/mid frequencies and at high frequency (11). In the present study, presence of CKD was associated with 1.8-fold higher prevalence of total prevalence of moderate HI and 1.9-fold higher prevalence of moderate HI at 4 kHz.

A study of Hispanic/Latina men and women examined the associations between risk factors and HI according to the number of ears with HI. It showed that the associations between risk factors and HI were similar in both bilateral HI and total HI. Diabetes mellitus was positively associated with the risk of total HI and bilateral HI (8). In the present study, the same associations were observed, though the association between diabetes mellitus and prevalence of unilateral HI was not significant.

The mechanism for the association between proteinuria and HI is uncertain, but our findings and findings from previous studies imply that microvascular damage may lead to HI. The blood vessel that brings oxygen and nutrition to the inner ear is the labyrinthine artery. This artery is a thin branch of the anterior inferior cerebellar artery. Therefore, the microvascular damage caused by atherosclerosis may be associated with

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prevalence of HI. In the present study, proteinuria of 2+ or more was positively associated with the risk of unilateral HI. We assumed that proteinuria of 2+ or more might imply the existence of damaged vessels throughout the body. A study in Canadians showed that the risk of cardiovascular events increased with higher levels of proteinuria independent of eGFR level (15). The association between proteinuria and bilateral HI was not significant, but this was likely because of the small number of cases. However, diabetes mellitus was significantly associated with prevalence of bilateral HI, but not unilateral HI. We assumed that diabetes mellitus may have other effects such as glucose toxicity as well as atherosclerosis in the inner ear.

The present study had some limitations. First, the present study could not establish a causal relationship because of its cross-sectional design. Second, this study was based on results of annual health check-up in a company, therefore, our results could not generalize easily. Third, it was carried out based on annual health check-ups that are prescribed by Japanese law. Therefore, we were unable to information on hearing tests other than 1 kHz and 4 kHz and precise thresholds for each frequency. Fourth, we were not able to evaluate the history of noise exposure in workplaces before 2008 because the data were anonymous and did not contain a precise history with regard to HI. Therefore, the present study did not evaluate the effect of noise exposure in detail, although we adjusted for the possibility of noise exposure when subjects carried out annual health check-ups between 2008 and 2016. Lastly, we did not have information on alcohol intake because the dataset did not include it. However, gamma-GT, the elevation of which is usually associated with ingestion of alcohol, was not associated with HI prevalence.

In conclusion, dipstick proteinuria was positively associated with the

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prevalence of moderate HI in Japanese workers. Diabetes mellitus and CKD were also associated with the prevalence of moderate HI. Although no causal relationship can be inferred, these results suggest that medical examination for cardiovascular disease prevention may also effective in detecting subjects who are at high risk of HI.

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Contributors

MU, MH and GK designed this study. MU and MH made data set. MU, TS, YH, MN, MM and GK analyzed the data. MU wrote the first draft of the manuscript. MH, TS, YH, MN, MM and GK commented on the manuscript.

Competing interests

None declared.

Data sharing statement

No additional data are available.

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Table 1 Age- and sex-adjusted characteristics of subjects according to presence of moderate hearing impairment

	Subjects without moderate hearing impairment (N=5868)		Subjects with moderate hearing impairment (N=324)		*P* for ANOVA/ ANCOVA
	N	Mean ± SE	N	Mean ± SE	
Age (y.o.)	5868	44.5 ± 0.1	324	52.5 ± 0.5	<0.01
Men (%)		87.8		96.0	
Body mass index (kg/m^2)	5854	23.4 ± 0.0	324	23.5 ± 0.2	0.61
Waist (cm)	5844	82.9 ± 0.1	324	83.5 ± 0.5	0.31
Systolic blood pressure (mmHg)	5868	116.7 ± 0.2	324	118.2 ± 0.8	0.06
Diastolic blood pressure (mmHg)	5868	72.9 ± 0.1	324	73.5 ± 0.6	0.34
Medication for hypertension (%)	5866	9.9	324	12.3	0.15
Total cholesterol (mg/dl)	5865	198.9 ± 0.4	324	196.9 ± 1.8	0.27
LDL cholesterol (mg/dl)	5867	120.6 ± 0.4	324	118.6 ± 1.7	0.24
HDL cholesterol (mg/dl)	5867	56.7 ± 0.2	324	56.9 ± 0.8	0.77
Triglyceride (mg/dl)	5866	120.8 ± 1.2	324	120.7 ± 5.2	0.98
Medication for hypercholesterolemia (%)	5866	6.4	324	8.5	0.14
HbA1c (NGSP)(%)	5838	5.5 ± 0.0	324	5.6 ± 0.0	0.01
Medication for diabetes mellitus (%)	5864	3.4	324	6.7	<0.01
Creatinine (mg/dl)	5864	0.8 ± 0.0	324	0.9 ± 0.0	<0.01
Aspartate transaminase (U/L)	5866	23.0 ± 0.1	324	24.7 ± 0.6	0.01
Alanine transaminase (U/L)	5867	26.0 ± 0.3	324	26.4 ± 1.2	0.78
Gamma-glutamyl transpeptidase (U/L)	5867	44.8 ± 0.7	324	50.9 ± 2.8	0.04
Hemoglobin (g/dl)	5866	15.0 ± 0.0	324	15.0 ± 0.1	0.77
Current smoker (%)	5857	69.8	323	68.5	0.59
Proteinuria of 1+ or more (%)	5863	3.6	323	6.9	<0.01
Urine glocose of 1+ or more (%)	5863	1.8	323	3.4	0.05
Working in noisy place between 2008-2016 (%)	5868	12.5	324	15.2	0.14
Patients with hearing impairment at 1 kHz		-		107	-
Patients with hearing impairment at 4 kHz		-		278	-
Patients with hearing impairment at 1 kHz and/or 4 kHz		-		324	-

Table 2 Age- and sex-adjusted characteristics of subjects according to degree of proteinuria

	Degree of proteinuria								*P* for ANOVA/ ANCOVA
	(-) (N=5103)		(+-) (N=851)		(+) (N=198)		(≥2+) (N=34)		
	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE	
Age (y.o.)		45.0 ± 0.1		44.3 ± 0.3		45.0 ± 0.7		50.9 ± 1.6	<0.01
Men (%)		88.1		89.1		88.4		100.0	0.16
Body mass index (kg/m^2)	5093	23.4 ± 0.0	847	23.4 ± 0.1	198	24.3 ± 0.2	34	24.9 ± 0.6	<0.01
Waist (cm)	5083	82.8 ± 0.1	848	82.9 ± 0.3	197	85.6 ± 0.6	34	86.8 ± 1.6	<0.01
Systolic blood pressure (mmHg)	5103	116.7 ± 0.2	851	116.4 ± 0.5	198	117.8 ± 1.0	34	124.1 ± 2.3	<0.01
Diastolic blood pressure (mmHg)	5103	72.8 ± 0.1	851	73.2 ± 0.4	198	74.6 ± 0.7	34	78.5 ± 1.8	<0.01
Medication for hypertension (%)	5103	9.4	850	10.5	198	19.1	33	39.7	<0.01
Total cholesterol (mg/dl)	5101	198.4 ± 0.5	851	200.5 ± 1.1	197	203.3 ± 2.3	34	199.3 ± 5.6	0.07
LDL cholesterol (mg/dl)	5102	120.2 ± 0.4	851	121.9 ± 1.0	198	124.0 ± 2.1	34	121.1 ± 5.2	0.17
HDL cholesterol (mg/dl)	5102	56.9 ± 0.2	851	56.5 ± 0.5	198	53.5 ± 1.0	34	52.8 ± 2.4	0.02
Triglyceride (mg/dl)	5102	119.2 ± 1.3	851	123.3 ± 3.2	197	145.4 ± 6.5	34	149.5 ± 15.8	<0.01
Medication for hypercholesterolemia (%)	5103	6.3	850	6.0	198	9.0	33	35.8	<0.01
HbA1c (NGSP)(%)	5101	5.5 ± 0.0	849	5.6 ± 0.0	197	5.7 ± 0.0	34	6.0 ± 0.1	<0.01
Medication for diabetes mellitus (%)	5102	3.2	849	3.3	198	9.1	33	22.5	<0.01
Creatinine (mg/dl)	5101	0.8 ± 0.0	850	0.8 ± 0.0	197	0.8 ± 0.0	34	1.5 ± 0.0	<0.01
Aspartate transaminase (U/L)	5102	22.8 ± 0.2	850	23.7 ± 0.4	198	27.6 ± 0.8	34	21.7 ± 1.9	<0.01
Alanine transaminase (U/L)	5102	25.6 ± 0.3	851	27.0 ± 0.7	198	33.7 ± 1.5	34	24.4 ± 3.5	<0.01
Gamma-glutamyl transpeptidase (U/L)	5102	44.4 ± 0.7	851	47.0 ± 1.7	198	56.4 ± 3.6	34	63.8 ± 8.6	<0.01
Hemoglobin (g/dl)	5102	15.0 ± 0.0	851	15.0 ± 0.0	197	15.3 ± 0.1	34	14.6 ± 0.2	<0.01
Current smoker (%)	5095	70.1	849	68.5	197	69.4	33	65.6	0.72
Urine glocose 1+ or more (%)	5103	1.7	851	2.1	198	5.0	34	8.0	<0.01
Working in noisy place between 2008-2016 (%)	5103	11.3	851	20.9	198	11.7	34	9.4	<0.01
Patients with hearing impairment at 1 kHz	5103	88	851	11	198	5	34	3	-
Patients with hearing impairment at 4 kHz	5103	227	851	31	198	11	34	8	-
Patients with hearing impairment at 1 kHz and/or 4 kHz	5103	262	851	38	198	14	34	9	-

Table 3 Relationships between cardiovascular risk factors and prevalence of hearing impairment

	Prevalence of hearing impairment (%)											
	30dB< in 1kHz and/or 40dB< in 4kHz (total moderate HI)				30dB< in 1kHz				40dB< in 4kHz			
	Age, sex-adjusted		Multivariable-adjusted		Age, sex-adjusted		Multivariable-adjusted		Age, sex-adjusted		Multivariable-adjusted	
	Case/N	Prevalence(%)	Case/N	Prevalence(%)	Case/N	Prevalence(%)	Case/N	Prevalence(%)	Case/N	Prevalence(%)	Case/N	Prevalence(%)
Proteinuria[1]												
-	262/5103	5.1%	262/5091	5.2%	88/5103	1.7%	88/5091	1.7%	227/5103	4.4%	227/5091	4.4%
+-	38/851	4.7%	38/845	4.6%	11/851	1.4%	11/845	1.4%	31/851	3.8%	31/845	3.7%
+	14/198	7.0%	14/197	6.8%	5/198	2.5%	5/197	2.5%	11/198	5.5%	11/197	5.4%
≥2+	9/34	23.7%	9/34	22.9%	3/34	8.1%	3/34	8.0%	8/34	21.1%	8/34	20.5%
P for ANCOVA		<0.01		<0.01		0.02		0.03		<0.01		<0.01
Diabetes mellitus[2]												
No	286/5843	5.1%	286/5829	5.1%	96/5843	1.7%	-	-	247/5843	4.4%	-	-
Yes	38/344	8.2%	38/344	7.8%	11/344	2.4%	-	-	31/344	6.5%	-	-
P for ANCOVA		0.01		0.03		0.33		-		0.06		-
Hypertension												
No	228/5144	5.0%	-	-	82/5144	1.8%	-	-	196/5144	4.3%	-	-
Yes	96/1048	6.4%	-	-	25/1048	1.6%	-	-	82/1048	5.4%	-	-
P for ANCOVA		0.08		-		0.71		-		0.15		-
Urinary glucose												
-	306/6039	5.1%	-	-	101/6039	1.7%	-	-	264/6039	4.4%	-	-
+-	3/28	8.0%	-	-	1/28	2.9%	-	-	2/28	4.7%	-	-
+	3/31	7.5%	-	-	0/31	0.0%	-	-	3/31	7.7%	-	-
≥2+	11/88	9.7%	-	-	5/88	4.9%	-	-	8/88	6.6%	-	-
P for ANCOVA		0.21		-		0.09		-		0.62		-
Serum creatinine[3]												
Q1(low)	85/1552	5.5%	-	-	25/1552	1.6%	-	-	71/1552	4.6%	-	-
Q2	76/1602	5.2%	-	-	27/1602	1.8%	-	-	65/1602	4.5%	-	-
Q3	73/1679	4.2%	-	-	21/1679	1.3%	-	-	65/1679	3.7%	-	-
Q4(high)	90/1355	6.2%	-	-	34/1355	2.3%	-	-	77/1355	5.3%	-	-
P for ANCOVA		0.11		-		0.18		-		0.22		-

[1] Adjusted for age, sex, body mass index (kg/m2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine (sex-specific quintile) and history of noisy work environment between 2008-2016 (yes or no) for calculation for multivariable-adjusted prevalence of HI

[2] Adjusted for age, sex, body mass index (kg/m^2), hypertension (yes or no), proteinuria (yes or no), serum creatinine (sex-specific quintile) and history of noisy work environment between 2008-2016 (yes or no) for calculation for multivariable-adjusted prevalence of HI

[3] sex-specific quartile

Table 4 Associations between hearing impairment and proteinuria and diabetes mellitus according to number of ears with hearing impairment

	Prevalence of total moderate hearing impairment in one ear				Prevalence of total moderate hearing impairment in two ears			
	Age-, sex-adjusted		Multivariable-adjusted		Age, sex-adjusted		Multivariable-adjusted	
	Case/N	Prevalence(%)	Case/N	Prevalence(%)	Case/N	Prevalence(%)	Case/N	Prevalence(%)
Proteinuria[1]								
-	176/5103	3.4	176/5091	3.5	86/5103	1.7	86/5091	1.7
+-	25/851	3.0	25/845	3.0	13/851	1.6	13/845	1.6
+	10/198	5.0	10/197	4.9	4/198	2.0	4/197	1.9
≥2+	7/34	18.9	7/34	18.4	2/34	4.8	2/34	4.5
P for ANCOVA		<0.01		<0.01		0.54		0.64
Diabetes mellitus[2]								
No	195/5843	3.4	195/5829	3.5	91/5843	1.6	91/5829	1.6
Yes	23/344	5.0	23/344	4.6	15/344	3.2	15/344	3.2
P for ANCOVA		0.14		0.28		0.02		0.03

[1] Adjusted for age, sex, body mass index (kg/m^2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine (sex-specific quintile) and history of noisy work environment between 2008-2016 (yes or no) for calculation for multivariable-adjusted prevalence of HI

[2] Adjusted for age, sex, body mass index (kg/m^2), hypertension (yes or no), proteinuria (yes or no), serum creatinine (sex-specific quintile) and history of noisy work environment between 2008-2016 (yes or no) for calculation for multivariable-adjusted prevalence of HI

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, Tables 1-4
		(b) Give reasons for non-participation at each stage	N/A (12-(c):Page 9)
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Tables 1-4
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between dipstick proteinuria and hearing impairment in health check-ups among Japanese workers: a cross-sectional study

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Abstract

Objective: Prevention of hearing impairment is important because it is difficult to recover from it. Epidemiological studies have examined the risk factors for hearing impairment; however, the association between dipstick proteinuria and hearing impairment has not been previously examined. This study aimed to clarify the association between dipstick proteinuria and hearing impairment.

Design: Cross-sectional study**.**

Setting: Office and factory workers from all over Japan.

Participants: The total number of subjects was 7,005. All were employees of the same company. Of these, we recruited 6,192 subjects who underwent dipstick urine test and hearing test by audiometry in annual health checkups (mean age 44.9 years, men 88.3%).

Primary Outcomes: Hearing tests were performed at two frequencies (1 kHz, 4 kHz) as prescribed by law in Japan. We defined inability of subjects to respond to 30 dB at 1 kHz and/or 40 dB at 4 kHz as overall moderate hearing impairment. In addition, we defined moderate hearing impairment at 1 kHz (4 kHz) as an abnormal finding at 1 kHz (4 kHz). We examined the associations between degree of dipstick proteinuria and hearing impairment after adjustment for age, sex, body mass index, hypertension, diabetes mellitus, serum creatinine level and history of noisy work environment.

Results: Overall moderate hearing impairment was noted in 324 subjects (5.2%). Of these, 107 subjects (1.7%) had moderate hearing impairment at 1 kHz and 278 subjects (4.5%) at 4 kHz. Dipstick proteinuria was significantly associated with overall moderate hearing impairment, as well as moderate hearing impairment at both 1 kHz and 4 kHz. The prevalence of overall moderate hearing impairment among subjects with proteinuria

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≥2+ was 23.5%, while that among subjects without proteinuria was 5.2% (P <0.01).

Conclusions: Dipstick proteinuria was associated with moderate hearing impairment in Japanese workers.

(290/300 words)

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Strength and limitations of this study

- This study was based on annual health check-ups conducted according to Japanese law. Therefore, study participants comprised both healthy and unhealthy workers.
- Our research was unable to use precise information on hearing tests compared with tests conducted in hospitals because this study is based on health check-ups that are mandated by law.

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Introduction

Hearing impairment (HI) is a common symptom among older people. According to the World Health Organization (WHO) fact sheet published in February 2017, almost one-third of older people aged 65 years or over have HI. Prevention of HI is important in public health not only because HI is a condition that makes communication difficult, but also because it is associated with the risk of dementia (1-3). A recent review reported that hearing loss in midlife (45–65 years old) was also associated with the risk of dementia (4).

Recovery from HI is difficult. Therefore, several epidemiological studies aimed at finding risk factors for HI have been carried out. They identified many risk factors such as aging, exposure to loud noises, and medications. Of these, many studies examined associations between lifestyle-related diseases involving microvascular disorders and HI. A meta-analysis of 13 cross-sectional studies suggested that a higher prevalence of HI was observed in diabetic patients compared with non-diabetic patients (5). With regard to hypertension, a study in a Korean population showed a positive association between hypertension and the risk of HI (6). A case-control study of Brazilians also showed a positive association between hypertension and hearing loss (7). In a similar study conducted among Hispanics/Latinos in United States, no such association was found (8). For serum lipids, compared with men who had a lower high-density lipoprotein (HDL) cholesterol concentration, hearing levels at high frequencies were significantly better among men with a higher HDL cholesterol concentration (9). Recently, a cross-sectional study of Korean subjects showed that albuminuria, low-grade albuminuria, urine albumin creatinine ratio, and eGFR were associated with HI among non-diabetic subjects (10-12). However, the association

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between HI and dipstick proteinuria, a test commonly performed in health checks, has not been examined yet.

Therefore, we aimed to examine the association between dipstick proteinuria and prevalence of HI. If dipstick proteinuria were associated with HI, the dipstick urine test would be beneficial in detecting individuals with a high risk of HI. We hypothesize that the degree of dipstick proteinuria is positively associated with HI. To test our hypothesis, we conducted an association study among Japanese workers.

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Method

Subjects

The subjects were 19-to-66-year-old employees of Japan Tobacco Inc. (JT). All subjects worked in offices and/or factories throughout Japan. There were 7,005 subjects in total (6,039 men and 966 women). They underwent annual health check-ups between 2008 and 2016. In subjects who had undergone annual health check-ups twice or more, we used the latest data for the analyses. We excluded 813 subjects from the analysis who did not undergo hearing test by audiometry. Therefore, we used data from 6,192 subjects (5,466 men and 726 women) in the analyses.

We used anonymized data with the permission of JT. The study was approved by the Ethics Committee of Dokkyo Medical University (Univ-28018).

Risk factor survey

The annual health check-up was conducted as required by the Industrial Safety and Health Act under Japanese law. The check-up consisted of a body height and weight measurement with light clothing, ascertaining medical history, alcohol consumption/smoking status, a hearing test, a vision test, blood pressure measurement, blood tests, and dipstick urine tests. Dipstick urine tests were not performed with any specific timing. The hearing test was performed using audiometry. In accordance with Japanese law, two categories of hearing tests were applied at 1 kHz and 4 kHz for each ear. Inability to respond to 30 dB at 1 kHz and/or 40 dB at 4 kHz was defined as the threshold for “abnormal”. Blood pressure was measured using automated sphygmomanometers. eGFR was calculated using the following formula established by the working group of the Japanese Chronic Kidney Disease Initiative: eGFR

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(mL/min/1.73m^2) = 1.94 × (serum creatinine)−1.094 × (age)−0.287 × 0.739 (if female) (13). For HbA1c, the National Glycohemoglobin Standardization Program [NGSP] value was used for most subjects. For 25 subjects, only the Japan Diabetes Society [JDS] value was available, and therefore we adapted their value to the NGSP value using the conversion formula as follows; HbA1c (NGSP) = 1.02 × HbA1c (JDS) + 0.25% (14).

Definition of variables

We classified subjects according to degree of proteinuria: -, +-, + and ≥2+. For hearing impairment, we defined a subject as having overall moderate hearing impairment (overall moderate HI), if there was an abnormal finding in any one category. Likewise, we defined moderate HI at 1 kHz (4 kHz) as an abnormal finding at 1 kHz (4 kHz). For other variables, we defined hypertension as ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure and/or taking medication for hypertension, and defined diabetes mellitus as ≥6.5% HbA1c and/or taking medication for diabetes mellitus. Body mass index (BMI) was calculated as follows: weight in kilograms divided by height in meters squared. Serum creatinine level was classified by using sex-specific quintiles. We defined CKD as eGFR <60 (mL/min/1.73m^2) and/or proteinuria 2+ or more.

Statistical analysis

We calculated the characteristics of subjects according to degree of proteinuria. The characteristics included variables as age, sex, BMI, systolic and diastolic blood pressure, blood test, dipstick urine glucose test, current smoking, history of working in a noisy

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place between 2008–2016 and medication for hypertension, hypercholesterolemia, and diabetes mellitus. Blood test included HbA1c level and serum creatinine level. We used variables that showed significant difference according to degree of proteinuria for confounding variable except for age and sex. We calculated age and sex-adjusted prevalence of overall moderate HI and moderate HI at 1 kHz and 4 kHz according to degree of proteinuria (-, +-, + and ≥2+). We also calculated multivariable-adjusted prevalence of moderate HI. We used confounding variables for adjustment that included age, sex, BMI (kg/m^2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine level (sex-specific quintiles) and noisy work environment between 2008-2016 (yes or no). We also examined the association according to number of ears that were regarded as 'abnormal'. In addition to the associations between dipstick proteinuria and moderate HI, we examined the association between chronic kidney disease (CKD) and moderate HI. We tested for sex interaction in each analysis and found no significant interactions.

We used SAS version 9.4 software (SAS Institute, Cary, NC) for all analyses. We excluded subjects from analysis if subjects had any missing. *P* values <0.05 were regarded as statistically significant.

Patient and Public involvement

This study did not involve patient and public.

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Results

In the present study, among 6,192 subjects, 324 subjects (5.2%) had overall moderate HI. A total of 107 subjects (1.7%) had moderate HI at 1 kHz and 278 subjects (4.5%) had moderate HI at 4 kHz. A total of 61 subjects (1.0%) had HI at both 1 kHz and 4 kHz. Among 324 subjects with overall moderate HI, 218 subjects (3.5%) had moderate HI in one ear and 106 subjects (1.7%) had moderate HI in two ears.

Table 1 shows the characteristics of subjects according to the degree of proteinuria. Compared with subjects who did not have proteinuria, subjects with proteinuria of 2+ or more showed higher age, BMI, blood pressure, HbA1c level, proportion of dipstick urine glucose, and proportion taking medication for hypertension and/or diabetes mellitus.

Table 2 shows the prevalence of moderate HI according to the degree of dipstick proteinuria. Proteinuria was positively associated with overall moderate HI and its subtypes. The prevalence of overall moderate HI among subjects with proteinuria of 2+ or more was 23.5%, while that among subjects who did not have proteinuria was 5.2% (*P* for difference <0.01). The prevalence of moderate HI at 1 kHz and 4 kHz among subjects with proteinuria of 2+ or more was 8.2% and 21.1%, respectively, while that among subjects who did not have proteinuria was 1.7% and 4.5% (*P* for difference were <0.01 and <0.01).

Table 3 shows associations between prevalence of overall moderate HI and proteinuria and diabetes mellitus according to the number of ears with HI. Proteinuria was positively associated with overall moderate HI in one ear, but not in two ears.

We also examined the association between CKD and moderate HI. Presence of CKD was significantly associated with overall moderate HI and moderate HI at 4 kHz.

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After adjustment for age, sex, BMI, hypertension, diabetes mellitus and noisy work environment, the prevalence of overall moderate HI among subjects with CKD was 8.9%, whereas it was 5.1% among subjects without CKD (*P* for difference <0.01). The prevalence of moderate HI at 4 kHz was 8.1% among subjects with CKD, and it was 4.3% among subjects who without CKD (P for difference <0.01).

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Discussion

In the present study, we found that subjects with dipstick proteinuria of 2+ or more showed significantly higher prevalence of HI in all ranges, and at 1 kHz and 4 kHz, compared with subjects without dipstick proteinuria. Subjects with CKD also showed a higher prevalence of HI compared with subjects without CKD.

A previous study on Korean subjects showed a positive association between albuminuria and prevalence of HI (10). In this study, degree of albuminuria was significantly associated with moderate to severe HI defined as a hearing threshold level for the superior ear of ≥40 dB, both in low/mid (0.5, 1.0, and 2.0 kHz) and high (3.0, 4.0, and 6.0 kHz) frequencies. However, the association between albuminuria and mild HI defined as a hearing threshold level for the superior ear of 26-40 dB was not significant. Subjects with albuminuria had 1.5-fold higher prevalence of moderate to severe HI at frequency ranges 1.7-fold higher at low/mid frequency and 1.3-fold higher at high frequency (10). The present study revealed similar associations between dipstick proteinuria level and HI. We recalculated to examine the association between dipstick proteinuria of 1+ or more and the prevalence of HI, and found that dipstick proteinuria of 1+ or more was also significantly associated with overall moderate HI and moderate HI at 4 kHz, but not moderate HI at 1 kHz (data not shown).

The mechanism for the association between proteinuria and HI is uncertain, but our findings and findings from previous studies imply that microvascular damage may lead to HI. The blood vessel that brings oxygen and nutrition to the inner ear is the labyrinthine artery. This artery is a thin branch of the anterior inferior cerebellar artery. Therefore, the microvascular damage caused by atherosclerosis may be associated with prevalence of HI. In the present study, proteinuria of 2+ or more was positively

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associated with the risk of unilateral HI. We assumed that proteinuria of 2+ or more might imply the existence of damaged vessels throughout the body. A study in Canadians showed that the risk of cardiovascular events increased with higher levels of proteinuria independent of eGFR level (15). The association between proteinuria and bilateral HI was not significant, but this was likely because of the small number of cases.

The present study had some limitations. First, the present study could not establish a causal relationship because of its cross-sectional design. Second, this study was based on results of annual health check-up in a company; therefore, our results could not generalize easily. Third, it was carried out on the basis of annual health check-ups that are prescribed by Japanese law. Therefore, we were unable to obtain information on hearing tests other than 1 kHz and 4 kHz and precise thresholds for each frequency. Fourth, we were not able to evaluate the history of noise exposure in workplaces before 2008 because the data were anonymous and did not contain a precise history with regard to HI. Therefore, the present study did not evaluate the effect of noise exposure in detail, although we adjusted for the possibility of noise exposure when subjects underwent annual health check-ups between 2008 and 2016. Fifth, we could not specify the timing for when urine was taken. Therefore, our results may have been affected by fluctuations in proteinuria and other variables. However, any errors concerning the misclassification were non-differential. Lastly, we did not have information on alcohol intake because the dataset did not include it. However, gamma-GT, the elevation of which is usually associated with ingestion of alcohol, was not associated with HI prevalence (data not shown).

In conclusion, dipstick proteinuria was associated with moderate HI in

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Japanese workers. Further studies are necessary to confirm this finding.

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Contributors

MU, MH and GK designed this study. MU and MH made data set. MU, TS, YH, MN, MM and GK analyzed the data. MU wrote the first draft of the manuscript. MH, TS, YH, MN, MM and GK commented on the manuscript.

Competing interests

None declared.

Data sharing statement

No additional data are available.

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Table 1 Age- and sex-adjusted characteristics of subjects according to degree of proteinuria

	Degree of proteinuria								*P* for ANOVA/ ANCOVA
	(-) (N=5103)		(+-) (N=851)		(+) (N=198)		(≥2+) (N=34)		
	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE	
Age (y.o.)		45.0 ± 0.1		44.3 ± 0.3		45.0 ± 0.7		50.9 ± 1.6	<0.01
Men (%)		88.1		89.1		88.4		100.0	0.16
Body mass index (kg/m^2)	5093	23.4 ± 0.0	847	23.4 ± 0.1	198	24.3 ± 0.2	34	24.9 ± 0.6	<0.01
Systolic blood pressure (mmHg)	5103	116.7 ± 0.2	851	116.4 ± 0.5	198	117.8 ± 1.0	34	124.1 ± 2.3	<0.01
Diastolic blood pressure (mmHg)	5103	72.8 ± 0.1	851	73.2 ± 0.4	198	74.6 ± 0.7	34	78.5 ± 1.8	<0.01
Medication for hypertension (%)	5103	9.4	850	10.5	198	19.1	33	39.7	<0.01
HbA1c (NGSP)(%)	5101	5.5 ± 0.0	849	5.6 ± 0.0	197	5.7 ± 0.0	34	6.0 ± 0.1	<0.01
Medication for diabetes mellitus (%)	5102	3.2	849	3.3	198	9.1	33	22.5	<0.01
Creatinine (mg/dl)	5101	0.8 ± 0.0	850	0.8 ± 0.0	197	0.8 ± 0.0	34	1.5 ± 0.0	<0.01
Current smoker (%)	5095	70.1	849	68.5	197	69.4	33	65.6	0.72
Urine glocose 1+ or more (%)	5103	1.7	851	2.1	198	5.0	34	8.0	<0.01
Working in noisy place between 2008-2016 (%)	5103	11.3	851	20.9	198	11.7	34	9.4	<0.01
Patients with hearing impairment at 1 kHz	5103	88	851	11	198	5	34	3	-
Patients with hearing impairment at 4 kHz	5103	227	851	31	198	11	34	8	-
Patients with hearing impairment at 1 kHz and/or 4 kHz	5103	262	851	38	198	14	34	9	-

Table 2 Relationships between degree of proteinuria and hearing impairment

	Prevalence of hearing impairment (%)			
	Age, sex-adjusted		Multivariable-adjusted[1]	
	Case/N	Prevalence (%)	Case/N	Prevalence (%)
30dB< in 1kHz and/or 40dB< in 4kHz (overall moderate hearing impairment)				
Proteinuria				
-	262/5103	5.1	262/5090	5.2
+-	38/851	4.7	38/844	4.6
+	14/198	7	14/197	6.8
≥2+	9/34	23.7	9/33	23.5
P for ANCOVA		<0.01		<0.01
30dB< in 1kHz				
Proteinuria				
-	88/5103	1.7	88/5090	1.7
+-	11/851	1.4	11/844	1.4
+	5/198	2.5	5/197	2.5
≥2+	3/34	8.1	3/33	8.2
P for ANCOVA		0.02		0.03
40dB< in 4kHz				
Proteinuria				
-	227/5103	4.4	227/5090	4.5
+-	31/851	3.8	31/844	3.7
+	11/198	5.5	11/197	5.4
≥2+	8/34	21.1	8/33	21.1
P for ANCOVA		<0.01		<0.01

[1] Adjusted for age, sex, body mass index (kg/m^2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine (sex-specific quintile) and history of noisy work environment between 2008-2016 (yes or no) for calculation for multivariable-adjusted prevalence of hearing impairment

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Table 3 Associations between degree of proteinuria and hearing impairment according to number of ears

	Overall hearing impairment			
	Age-, sex-adjusted		Multivariable-adjusted[1]	
	Case/N	Prevalence (%)	Case/N	Prevalence (%)
In one ear				
Proteinuria				
-	176/5103	3.4	176/5090	3.5
+-	25/851	3.0	25/844	3.0
+	10/198	5.0	10/197	4.9
≥2+	7/34	18.9	7/33	18.9
P for ANCOVA		<0.01		<0.01
In two ears				
Proteinuria				
-	86/5103	1.7	86/5090	1.7
+-	13/851	1.6	13/844	1.6
+	4/198	2.0	4/197	1.9
≥2+	2/34	4.8	2/33	4.6
P for ANCOVA		0.54		0.62

[1] Adjusted for age, sex, body mass index (kg/m^2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine (sex-specific quintile) and history of noisy work environment between 2008-2016 (yes or no) for calculation for multivariable-adjusted prevalence of hearing impairment

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, Tables 1-3
		(b) Give reasons for non-participation at each stage	N/A (12-(c): Page 9)
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2, 3
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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