

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

Mitsumasa Umesawa,¹ Mikako Hara,² Toshimi Sairenchi,¹ Yasuo Haruyama,¹ Masanori Nagao,¹ Munehiro Matsushita,¹ Gen Kobashi¹

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¹Department of Public Health, Dokkyo Medical University, Tochigi, Japan

²Human Resources Services Division, Japan Tobacco, Tokyo, Japan

Correspondence to

Dr Mitsumasa Umesawa;
umesawa@dokkyomed.ac.jp

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 7005. All were employees of the same company. Of these, we recruited 6192 subjects who underwent dipstick urine test and hearing test by audiometry in annual health check-ups (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 the 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 $\geq 2+$ 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.

INTRODUCTION

Hearing impairment (HI) is a common symptom among older people. According to the WHO fact sheet published in February

Strengths and limitations of this study

- Little has been reported on the association between dipstick proteinuria and hearing impairment. Proteinuria may be one of the symptoms of micro-vessel damages.
- This study was based on annual health check-ups conducted according to Japanese law; therefore, the 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.

2017, almost one-third of older people aged 65 years or over have HI. Prevention of HI is important in public health because HI is a condition that makes communication difficult and it is associated with the risk of dementia.^{1–3} A recent review reported that hearing loss in mid-life (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 the risk factors for HI have been carried out. They identified many risk factors such as ageing, 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 patients with diabetes 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 the USA, 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 estimated glomerular filtration rate (eGFR) were associated with HI among non-diabetic subjects.^{10–12} However, the association 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 hypothesise that the degree of dipstick proteinuria is positively associated with HI. To test our hypothesis, we conducted an association study among Japanese workers.

METHODS

Subjects

The subjects were employees of Japan Tobacco (JT) aged 19–66 years old. All subjects worked in offices and/or factories throughout Japan. There were 7005 subjects in total (6039 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 in the analyses. We excluded 813 subjects from the analysis who did not undergo hearing test by audiometry. Therefore, we used data from 6192 subjects (5466 men and 726 women) in the analyses.

We used anonymised data with the permission of JT.

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 body height and weight measurements 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: $eGFR (mL/min/1.73 m^2) = 1.94 \times (\text{serum creatinine}) - 1.094 \times (\text{age}) - 0.287 \times 0.739$ (if female).¹³ For haemoglobin A1c (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: $HbA1c (NGSP) = 1.02 \times HbA1c (JDS) + 0.25\%$.¹⁴

Definition of variables

We classified subjects according to the degree of proteinuria: –, ±, + and ≥2+. For HI, we defined a subject as having 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. For other variables, we defined hypertension as ≥140 mm Hg systolic blood pressure and/or ≥90 mm Hg diastolic blood pressure and/or taking medications for hypertension, and defined diabetes mellitus as ≥6.5% HbA1c and/or taking medications for diabetes mellitus. Body mass index (BMI) was calculated as follows: weight in kilograms divided by height in metres squared. Serum creatinine level was classified using sex-specific quintiles. We defined chronic kidney disease (CKD) as eGFR <60 (mL/min/1.73 m²) and/or proteinuria 2+ or more.

Statistical analysis

We calculated the characteristics of subjects according to the degree of proteinuria. The characteristics included variables such as age, sex, BMI, systolic and diastolic blood pressure, blood test, dipstick urine glucose test, currently smoking, history of working in a noisy place between 2008 and 2016, and medications for hypertension and diabetes mellitus. Blood tests included HbA1c level and serum creatinine level. We used variables that showed significant difference according to the degree of proteinuria for confounding variables except for age and sex. We calculated the age-adjusted and sex-adjusted prevalence of overall moderate HI and moderate HI at 1 kHz and 4 kHz according to the degree of proteinuria (–, ±, + and ≥2+). We also calculated the multivariable-adjusted prevalence of moderate HI. We used confounding variables for adjustment that included age, sex, BMI (kg/m²), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine level (sex-specific quintiles) and noisy work environment between 2008 and 2016 (yes or no). We also examined the association according to the number of ears that were regarded as 'abnormal'. In addition to the associations between dipstick proteinuria and moderate HI, we examined the association between CKD and moderate HI. We tested for sex interaction in each analysis and found no significant interactions.

We used SAS V.9.4 software for all analyses. We excluded subjects from the analysis if they had any missing data. P values <0.05 were regarded as statistically significant.

Patient and public involvement

This study did not involve patients and the public.

RESULTS

In the present study, among 6192 subjects, 324 (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 (3.5%) had moderate HI in one ear and 106 (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 medications 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 was <0.01 and <0.01).

Table 3 shows the associations between the 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. The presence of CKD was significantly associated with overall moderate HI and moderate HI at 4 kHz. 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 without CKD (p for difference <0.01).

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, the 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

Table 1 Age-adjusted 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 (years)		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 (mm Hg)	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 (mm Hg)	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 glucose 1+ or more (%)	5103	1.7	851	2.1	198	5.0	34	8.0	<0.01
Working in a noisy place between 2008 and 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	–

ANCOVA, analysis of covariance; ANOVA, analysis of variance; HbA1c, haemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program.

Table 2 Relationships between degree of proteinuria and hearing impairment

	Prevalence of hearing impairment (%)			
	Age-adjusted, sex-adjusted		Multivariable-adjusted*	
	Case/N	Prevalence (%)	Case/N	Prevalence (%)
30 dB < in 1 kHz and/or 40 dB < in 4 kHz (overall moderate hearing impairment)				
Proteinuria				
–	262/5103	5.1	262/5090	5.2
±	38/851	4.7	38/844	4.6
+	14/198	7.0	14/197	6.8
≥2+	9/34	23.7	9/33	23.5
P for ANCOVA		<0.01		<0.01
30 dB < in 1 kHz				
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
40 dB < in 4 kHz				
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

*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 and 2016 (yes or no) for calculation of multivariable-adjusted prevalence of hearing impairment.

ANCOVA, analysis of covariance.

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 the 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.

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 the results of annual health check-ups in a company; therefore, our results could not be generalised 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 data set did not include it. However, gamma-glutamyl transferase, the elevation of which is

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

	Overall hearing impairment			
	Age-adjusted, sex-adjusted		Multivariable-adjusted*	
	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

*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 and 2016 (yes or no) for calculation of multivariable-adjusted prevalence of hearing impairment.

ANCOVA, analysis of covariance.

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

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

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Competing interests None declared.

Patient consent Not required.

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Data sharing statement No additional data are available.

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