BMJ Open

Relationships between dipstick proteinuria and risk of hearing impairment among Japanese workers: a prospective cohort study

Mitsumasa Umesawa,[1] Mikako Hara,[2] Toshimi Sairenchi,[1] Masanori Nagao,[1] Yasuo Haruyama,[1] Gen Kobashi[1]

[1]Department of Public Health, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan
[2]TS Network, Tokyo, Japan

Correspondence to
Dr Mitsumasa Umesawa;
umesawa@dokkyomed.ac.jp

ABSTRACT

Objectives Hearing impairment is among the most significant health problems, and the number of adults with hearing impairment is increasing worldwide. Therefore, the prevention of hearing impairment is important. Proteinuria appears to be a risk factor for hearing impairment, but no prospective studies have examined the association between proteinuria and hearing impairment risk. This prospective study aimed to clarify the association between dipstick proteinuria and risk of hearing impairment.

Design This was a prospective cohort study based on annual health check-up data, 2008–2016.

Setting Data were collected on 7005 employees of a single company who worked in offices and factories throughout Japan.

Participants We analysed data from 5699 subjects (88.6% men) who underwent annual health check-ups twice or more from 2008 to 2016, had no missing data, and were free from hearing impairment at baseline. We regarded the first health check-up as the baseline examination.

Primary and secondary outcome measures Hearing tests were performed using audiometry at two frequencies (1 and 4 kHz) during the health check-ups. Defining total moderate hearing impairment as the inability to respond to 30 dB at 1 kHz and/or 40 dB at 4 kHz, we examined the association between dipstick proteinuria at baseline and risk of hearing impairment at final examination.

Results Total moderate hearing impairment was noted in 162 (2.8%) subjects. Compared with subjects without proteinuria at baseline, the multivariable adjusted OR (95% CI) was 5.35 (1.87–15.25) for subjects with proteinuria ≥2+, 0.92 (0.40–2.13) for those with proteinuria +/−, and 1.33 (0.63–2.80) for those with proteinuria+ at baseline.

Conclusions Severe dipstick proteinuria was positively associated with risk of hearing impairment in the future. Our results suggest that medical examinations including urine testing are effective for detecting subjects with high risk of hearing impairment.

Strengths and limitations of this study

► This study was based on annual health check-ups conducted according to a legal requirement; therefore, the study participants consisted of both healthy and unhealthy people.
► Our research was unable to use precise hearing test results such as those produced by tests conducted in hospitals because this study was based on data from legally mandated health check-ups.
► Our study could not examine the relationship between hearing impairment and the cause of proteinuria because we did not have information on the cause of proteinuria.

than 40 dB in the better-hearing ear.[1] This number includes an estimated 432 million adults with HI, which is especially common among older people. Almost one-third of people aged 65 years or older have HI.[1]

Among older adults, HI makes communication difficult, and it has also been associated with increased risk of dementia.[2–4] A recent review reported that hearing loss in midlife (45–65 years old) was associated with the risk of dementia.[5] Dementia is an major health problem in industrial countries today and is expected to become an important health problem worldwide in the near future. A trial estimated that the number of people with dementia worldwide might reach 80 million by 2040.[6] Given its prevalence and consequences, the prevention of HI is clearly important for public health.

It is difficult to recover from HI. Therefore, several epidemiological studies aiming to find the risk factors for HI have been carried out. These studies have found many risk factors such as ageing, exposure to loud noises, diabetes mellitus, hypertension, lipid abnormality, medications and socioeconomic status.[7–12] Recently, a study in Taiwan showed

INTRODUCTION

According to a WHO fact sheet published in March 2018, 466 million people—over 5% of the world's population—have hearing impairment (HI), defined as hearing loss greater

that patients with end-stage renal disease had a higher risk of sudden sensorineural hearing loss, compared with controls.[13] Additionally, several epidemiological studies have reported that symptoms of renal injury, such as albuminuria, low-grade albuminuria, high urine albumin creatinine ratio, dipstick proteinuria, low estimated glomerular filtration rate and chronic kidney disease (CKD), were associated with higher risk of HI.[14–16] However, these studies have been unable to establish cause–effect relationships because of the studies' cross-sectional designs.

For several factors listed above, the precise mechanism of the association with HI is uncertain. However, the findings of previous studies lead us to suspect that vascular disorders such as atherosclerosis may be a cause of these associations. The labyrinthine artery, a thin branch of the anterior inferior cerebellar artery or basilar artery, is the main conduit for blood flow to the inner ear. Vascular disorders of the labyrinthine artery may lead to inner ear ischaemia.

In the present study, we examined the relationship between dipstick proteinuria and the incidence of HI using a prospective design. In addition to being a symptom of renal damage, dipstick proteinuria is an indicator of atherosclerosis.[17] We hypothesised that the degree of dipstick proteinuria is positively associated with HI incidence. To test our hypothesis, we conducted a prospective study among Japanese workers. If dipstick proteinuria is associated with the risk of HI, the dipstick urine test would be beneficial for identifying individuals at high risk of HI, which may lead to the prevention of HI.

METHODS

Subjects

Participants, aged 19–66 years, were employees of Japan Tobacco Inc. They worked in offices and factories all over Japan. There were 7005 participants in total (6039 men and 966 women). In the analyses, we used data from 5699 subjects (5048 men and 651 women) who underwent annual health check-ups twice or more from 2008 to 2016, did not have missing data and did not have HI at their first annual health check-up from 2008 to 2016. The precise numbers of subjects excluded and reasons for exclusion are shown in figure 1.

We used anonymized data with the permission of Japan Tobacco Inc.

Risk factor survey

Annual health check-ups were conducted from 2008 to 2016, as required by the Industrial Safety and Health Act in Japanese law. We regarded the first annual health check-up during this period as the baseline examination and the last annual health check-up during this period as the final examination. The precise details of the annual health check-ups have been described elsewhere.[18] In short, the check-up included a body weight measurement, medical history, alcohol consumption/smoking status, a hearing test, blood pressure measurement, blood tests, and dipstick urine tests. The hearing test was performed using audiometry. Following the Japanese legal requirement, two frequencies of hearing tests, 1 and 4 kHz, were carried out for each ear. Inability to respond to 30 dB at 1 kHz and/or 40 dB at 4 kHz was defined as the threshold
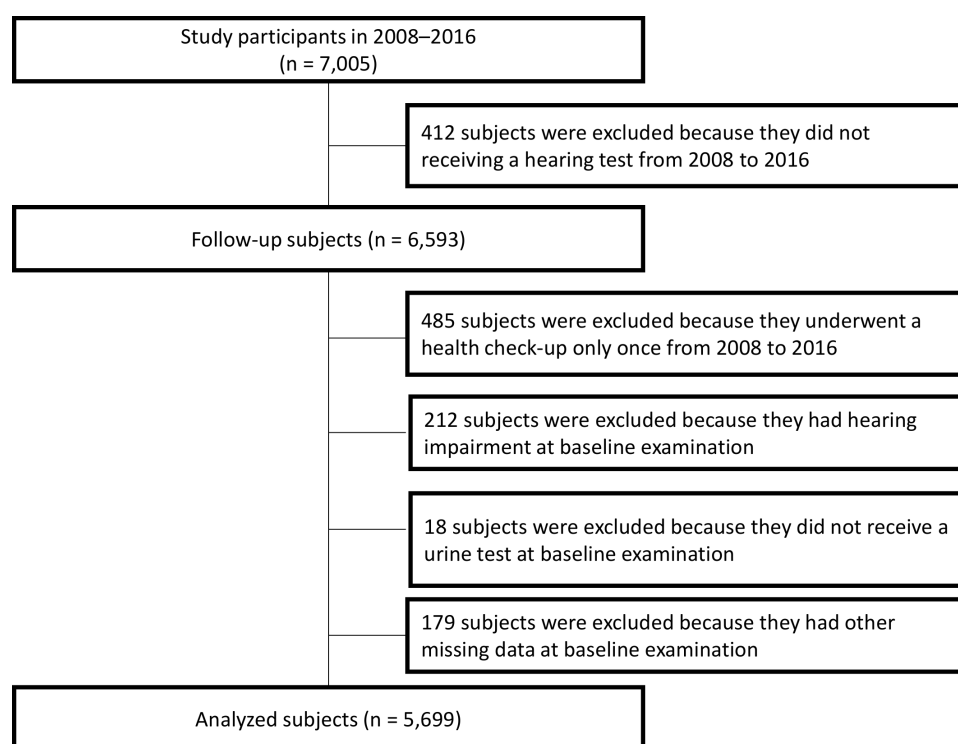

Figure 1 Study subjects.

for "abnormal." We defined total moderate HI as having an abnormal finding for either frequency in either ear at final examination. We defined moderate HI as having an abnormal finding at 1 kHz only, at 4 kHz only, and at both 1 and 4 kHz. For haemoglobin A1c (HbA1c), the National Glycohemoglobin Standardisation Program (NGSP) value has been used in Japan since 2015, and baseline HbA1c values were measured using the Japan Diabetes Society (JDS) value instead. We converted JDS values into NGSP values using the following conversion formula: HbA1c (NGSP)=1.02×HbA1c (JDS)+0.25%.[19]

Statistical analysis

Subjects' baseline characteristics assessed included calculated degree of proteinuria (−, +/−,+ or ≥2+), age, sex and age- and sex-adjusted means or proportions of cardiovascular risk factors such as body mass index (BMI), systolic and diastolic blood pressure, medication for hypertension, serum lipids, medication for hypercholesterolaemia, HbA1c level, medication for diabetes mellitus, serum creatinine level, hepatic enzymes, haemoglobin level, current smoking, dipstick urine glucose and history of working in a noisy place from 2008 to 2016. We defined hypertension as ≥140 mm Hg systolic blood pressure, ≥90 mm Hg diastolic blood pressure and/or taking medication for hypertension. We defined diabetes mellitus as ≥6.5% HbA1c (NGSP) and/or taking medication for diabetes mellitus.

We calculated OR for the risk of HI at final examination to evaluate the relationship between baseline proteinuria and risk of HI. We calculated ORs and 95% CIs for the risk of total moderate HI, moderate HI at 1 kHz and moderate HI at 4 kHz. We conducted the analyses in two ways because the number of subjects with severe proteinuria was limited. We first divided the subjects according to the presence of proteinuria (−, +/−, or ≥+). We then divided the subjects according to the degree of proteinuria (−, +/−, + or ≥2+). We used subjects whose degree of proteinuria at baseline examination was negative (−) as the reference category. When calculating the ORs, we adjusted for potentially confounding variables including age, sex, BMI, hypertension, diabetes mellitus, serum creatinine (sex-specific quartile) at baseline and noisy work environment from 2008 to 2016.

We used SAS V.9.4 software (SAS Institute) for all analyses. We used analysis of variance and analysis of covariance to evaluate differences in subjects' characteristics, and we used logistic regression models to calculate ORs and 95% CIs. We excluded subjects with any missing values from the analysis. P values <0.05 were regarded as statistically significant. We tested for sex interactions for all of the analyses but found no significant interactions.

Patient and public involvement

This study did not involve patients or the public.

Table 1 Age- and sex-adjusted characteristics of subjects at baseline examination

| | Degree of proteinuria | | | | | | | | p for ANOVA/ ANCOVA |
| | − (n=5180) | | ± (n=289) | | + (n=197) | | ≥2+ (n=33) | | |
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Age (years)	37.9	0.1	35.8	0.5	38.3	0.6	38.7	1.5	<0.01
Men (%)	88.6		85.8		91.9		81.8		0.12
Body mass index (kg/m^2)	22.9	0.0	22.8	0.2	23.6	0.2	25.1	0.6	<0.01
Systolic blood pressure (mm Hg)	115.3	0.2	113.7	0.8	117.7	0.9	121.4	2.2	<0.01
Diastolic blood pressure (mm Hg)	70.9	0.1	70.1	0.6	73.3	0.7	75.0	1.7	<0.01
Medication for hypertension (%)	2.9		4.1		6.4		27.0		<0.01
HbA1c (NGSP) (%)	5.3	0.0	5.3	0.0	5.4	0.0	5.7	0.1	<0.01
Medication for diabetes mellitus (%)	1.0		0.2		3.0		9.0		<0.01
Creatinine (mg/dL)	0.8	0.0	0.8	0.0	0.8	0.0	1.3	0.0	<0.01
Current smoker (%)	72.0		74.6		79.0		79.1		0.07
History of noisy work environment 2008–2016 (%)	14.2		12.7		11.1		19.4		0.35
Number of hearing impairment at 1 kHz	39		2		2		1		–
Number of hearing impairment at 4 kHz	113		5		7		4		–
Number of hearing impairment at 1 and/or 4 kHz	143		6		8		5		–

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

Table 2 Age- and sex-adjusted and multivariable-adjusted ORs of hearing impairment by the presence of proteinuria

	Age and sex adjusted		Multivariable adjusted*	
	Case/N	OR (95% CI)	Case/N	OR (95% CI)
>30 dB<at 1 kHz and/or>40 dB at 4 kHz (total moderate hearing impairment)				
Proteinuria				
–	143/5180	Reference	143/5180	Reference
+/–	6/289	0.92 (0.40 to 2.12)	6/289	0.92 (0.40 to 2.13)
≥+	13/230	1.99 (1.10 to 3.61)	13/230	1.85 (1.01 to 3.39)
>30 dB at 1 kHz				
Proteinuria				
–	39/5180	Reference	39/5180	Reference
+/–	2/289	1.06 (0.26 to 4.45)	2/289	1.10 (0.26 to 4.60)
≥+	3/230	1.68 (0.51 to 5.50)	3/230	1.31 (0.39 to 4.42)
>40 dB at 4 kHz				
Proteinuria				
–	113/5180	Reference	113/5180	Reference
+/–	5/289	1.00 (0.40 to 2.50)	5/289	1.00 (0.40 to 2.49)
≥ +	11/230	2.09 (1.10 to 3.99)	11/230	2.03 (1.06 to 3.92)

*The multivariable-adjusted prevalence of hearing impairment was calculated with adjustment for age, sex, body mass index (kg/m^2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine (sex-specific quintile) and current smoking status (yes or no) at baseline, as well as history of noisy work environment from 2008 to 2016 (yes or no).

RESULTS

In the present study, of the 5699 subjects, 162 (2.8%) had total moderate HI at final examination, including 44 (0.8%) with moderate HI at 1 kHz and 129 (2.3%) with moderate HI at 4 kHz. A total of 120 (2.1%) had moderate HI in one ear, and 42 (0.7%) had moderate HI in both ears. The median follow-up was 8 years, with a range of 1–8 years. A total of 74.5% of the subjects had a follow-up of 8 years.

Table 1 shows the subjects' characteristics at baseline examination. Compared with subjects who did not have proteinuria at baseline, subjects whose degree of proteinuria at baseline was ≥2+ had significantly higher BMIs, blood pressure levels, proportions of medication of hypertension, HbA1c levels, proportions taking medication for diabetes mellitus and serum creatinine levels.

Table 2 shows age- and sex-adjusted and multivariable-adjusted ORs of HI by the presence of proteinuria. The multivariable-adjusted OR for subjects with proteinuria was 1.85 (95% CI 1.01 to 3.39) for total moderate HI and 2.03 (95% CI 1.06 to 3.92) for moderate HI at 4 kHz. The association between the presence of proteinuria and risk of moderate HI at 1 kHz was not significant.

Table 3 shows age- and sex-adjusted and multivariable-adjusted ORs of HI by the degree of proteinuria. The degree of proteinuria was positively associated with the risk of total moderate HI and moderate HI at 4 kHz. For total moderate HI, the multivariable-adjusted OR for subjects whose degree of proteinuria was ≥2+ was 5.35 (95% CI 1.87 to 15.25). For moderate HI at 4 kHz, the multivariable-adjusted OR for subjects whose degree of

proteinuria was ≥2+ was 5.71 (95% CI 1.81 to 18.08). There was no significant association between degree of proteinuria and risk of moderate HI at 1 kHz.

DISCUSSION

In the present study, we found that subjects with proteinuria were at significantly higher risk of total moderate HI and moderate HI at 4 kHz, compared with subjects without proteinuria. This association was evident among subjects whose degree of proteinuria was ≥2+.

To our knowledge, no previous prospective cohort study has examined the association between proteinuria and the risk of HI. Several cross-sectional studies have examined the associations of albuminuria, low-grade albuminuria, urine albumin creatinine ratio, dipstick proteinuria, and CKD with the prevalence of HI.[14–16] In a previous study in Korea, subjects with albuminuria and low-grade albuminuria had a higher prevalence of moderate to profound HI overall and at low/middle and high frequencies.[14] Another study in Korea also showed that urine albumin creatinine ratio was positively associated with the prevalence of HI at low, middle and high frequencies and with the average hearing threshold,[15] and a third study in Korea showed that urine albumin creatinine ratio and lower estimated glomerular filtration rate as CKD stage 3 or more were positively associated with the prevalence of HI.[16] In a previous study, we found that the degree of dipstick proteinuria was positively associated with the prevalence of total moderate HI, moderate HI at 1 kHz, and moderate HI at 4 kHz.[18]

Table 3 Age- and sex-adjusted and multivariable-adjusted ORs of hearing impairment by the degree of proteinuria

	Age and sex adjusted		Multivariable adjusted*	
	Case/N	OR (95% CI)	Case/N	OR (95% CI)
>30 dB<at 1 kHz and/or>40 dB at 4 kHz (total moderate hearing impairment)				
Proteinuria				
−	143/5180	Reference	143/5180	Reference
+/−	6/289	0.92 (0.30 to 2.12)	6/289	0.92 (0.40 to 2.13)
+	8/197	1.41 (0.67 to 2.94)	8/197	1.33 (0.63 to 2.80)
≥2 +	5/33	5.99 (2.17 to 16.57)	5/33	5.35 (1.87 to 15.25)
>30 dB at 1 kHz				
Proteinuria				
−	39/5180	Reference	39/5180	Reference
+/−	2/289	1.06 (0.26 to 4.45)	2/289	1.09 (0.26 to 4.60)
+	2/197	1.32 (0.32 to 5.54)	2/197	1.07 (0.25 to 4.57)
≥2+	1/33	3.69 (0.49 to 28.05)	1/33	2.48 (0.31 to 20.07)
>40 dB at 4 kHz				
Proteinuria				
−	113/5180	Reference	113/5180	Reference
+/−	5/289	1.00 (0.40 to 2.50)	5/289	1.00 (0.40 to 2.49)
+	7/197	1.53 (0.70 to 3.38)	7/197	1.51 (0.68 to 3.33)
≥2 +	4/33	5.78 (1.89 to 17.68)	4/33	5.71 (1.81 to 18.08)

*The multivariable-adjusted prevalence of hearing impairment was calculated with adjustment for age, sex, body mass index (kg/m^2), hypertension (yes or no), diabetes mellitus (yes or no), serum creatinine (sex-specific quintile) and current smoking status (yes or no) at baseline, as well as history of noisy work environment from 2008 to 2016 (yes or no).

The present study's results differed from the results of these previous studies. The present study showed that the degree of proteinuria was positively associated with the risk of total moderate HI and moderate HI at 4 kHz, but not at 1 kHz. However, we could not conclude that there was no relationship between the degree of proteinuria and the risk of moderate HI at 1 kHz because of the small number of incidents of moderate HI at 1 kHz.

The mechanism of the association between proteinuria and the risk of HI is uncertain, but we assume that subjects who showed severe proteinuria had vascular damage. For example, a Japanese study reported the association between proteinuria and ankle-brachial index abnormality as an indicator of atherosclerosis.[17] The inner ear depends on the labyrinthine artery for oxygen and nutrition. This artery is a thin branch of the anterior inferior cerebellar artery or basilar artery. Therefore, vascular damage to the labyrinthine artery may lead to oxygen and nutrition deficiencies in the inner ear. Additionally, the structure of the cochlear and glomerular basement membranes may affect the association. A study on Alport syndrome revealed that the cochlear and glomerular basement membranes were rich in collagen IV.[20]

The strengths of the present study include the study design and the participants. First, we used a prospective cohort design, which guarantees the cause–effect relationship. Second, although the study participants were workers from one company, the present study included almost all workers at the selected company because annual health check-ups were carried out according to the law. Therefore, the present study appears to be a complete enumeration.

The study also had several limitations. First, our results cannot easily be generalised because participants in the present study were workers from one company. Second, we did not have precise hearing test data—only at 1 and 4 kHz—because these are the tests applied in the annual health check-ups prescribed by Japanese law. Third, in the present study, we could not detect the diagnosis or reason why proteinuria or HI were occurred because this study did not include information after health check-up. Therefore, we could not distinguish subjects who got HI caused by kidney disease such as focal segmental glomerulosclerosis (FSGS). Fourth, we adjusted for various risk factors concerned with vascular damage, however, we could not exclude influence of them completely. Finally, we were unable to specify the timing of urine collection; therefore, our results may have been affected by fluctuations in proteinuria and other variables. However, any errors concerning misclassification were non-differential.

CONCLUSIONS

Dipstick proteinuria was associated with the risk of moderate HI among Japanese workers, especially at 4kHz. Our findings suggest that the dipstick urine test would be beneficial for detecting subjects at high risk of HI incidence.

REFERENCES

1. WHO. Deafness and hearing loss. Available: http://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss [Accessed 6 Sep 2018].
2. Lin FR, Metter EJ, O'Brien RJ, *et al*. Hearing loss and incident dementia. *Arch Neurol* 2011;68:214–20.
3. Davies HR, Cadar D, Herbert A, *et al*. Hearing impairment and incident dementia: findings from the English longitudinal study of ageing. *J Am Geriatr Soc* 2017;65:2074–81.
4. Deal JA, Betz J, Yaffe K, *et al*. Hearing impairment and incident dementia and cognitive decline in older adults: the health ABC study. *J Gerontol A Biol Sci Med Sci* 2017;72:703–9.
5. Livingston G, Sommerlad A, Orgeta V, *et al*. Dementia prevention, intervention, and care. *Lancet* 2017;390:2673–734.
6. Ferri CP, Prince M, Brayne C, *et al*. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366:2112–7.
7. Horikawa C, Kodama S, Tanaka S, *et al*. Diabetes and risk of hearing impairment in adults: a meta-analysis. *J Clin Endocrinol Metab* 2013;98:51–8.
8. Hong JW, Jeon JH, Ku CR, *et al*. The prevalence and factors associated with hearing impairment in the Korean adults: the 2010-2012 Korea National health and nutrition examination survey (observational study). *Medicine* 2015;94:e611.
9. de Moraes Marchiori LL, de Almeida Rego Filho E, Matsuo T. Hypertension as a factor associated with hearing loss. *Braz J Otorhinolaryngol* 2006;72:533–40.
10. Cruickshanks KJ, Dhar S, Dinces E, *et al*. Hearing impairment prevalence and associated risk factors in the Hispanic community health Study/Study of Latinos. *JAMA Otolaryngol Head Neck Surg* 2015;141:641–8.
11. Scholes S, Biddulph J, Davis A, *et al*. Socioeconomic differences in hearing among middle-aged and older adults: cross-sectional analyses using the health survey for England. *BMJ Open* 2018;8:e019615.
12. Suzuki K, Kaneko M, Murai K. Influence of serum lipids on auditory function. *Laryngoscope* 2000;110:1736–8.
13. Wang I-K, Wang C-Y, Muo C-H, *et al*. Risk of sudden sensorineural hearing loss in patients with end-stage renal disease undergoing dialysis. *Nephrology* 2017;22:397–402.
14. Hong JW, CR K, Noh JH, *et al*. Association between hearing impairment and albuminuria in the Korean adults: the 2011-2012 Korea National health and nutrition examination survey. *Medicine*;2015:e1840.
15. Kang SH, Jung DJ, Choi EW, *et al*. Association between low-grade albuminuria and hearing impairment in a non-diabetic Korean population: the Korea National health and nutrition examination survey (2011-2013). *Ann Med* 2015;47:664–72.
16. Cho Y, Kim DH, Choi J, *et al*. Glomerular filtration rate and urine albumin to creatinine ratio associated with hearing impairment among Korean adults with diabetes: a nationwide population-based study. *Medicine* 2016;95:e3423.
17. Ishida A, Nakachi-Miyagi M, Kinjo K, *et al*. A high normal Ankle-brachial index is associated with proteinuria in a screened cohort of Japanese: the Okinawa peripheral arterial disease study. *J Hypertens* 2014;32:1435–43.
18. Umesawa M, Hara M, Sairenchi T, *et al*. Association between dipstick proteinuria and hearing impairment in health check-ups among Japanese workers: a cross-sectional study. *BMJ Open* 2018;8:e021427.
19. Kashiwagi A, Kasuga M, Araki E, *et al*. International clinical harmonization of glycated hemoglobin in Japan: from Japan diabetes Society to national Glycohemoglobin standardization program values. *J Diabetes Investig* 2012;3:39–40.
20. Miner JH, Baigent C, Flinter F, *et al*. The 2014 International workshop on Alport syndrome. *Kidney Int* 2014;86:679–84.