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Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large occupational health check-up data of Japan

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Objectives The aim of this study was to determine whether hemoglobin A1c (HbA1c) level is associated with the incidence of hearing impairment accounting for smoking status and diabetic condition at baseline.

Methods Participants were 131,689 men and 71,286 women aged 30-65 years and free of hearing impairment at baseline (2008) who attended annual health check-ups from 2008 to 2015. We defined low frequency hearing impairment at a hearing threshold >30 dB at 1 kHz and high frequency at >40 dB at 4 kHz in the better ear in pure-tone audiometric tests. HbA1c was categorized into 7 categories. The association between HbA1c and hearing impairment was assessed using the Cox proportional hazards model.

Results On 5 years' mean follow-up, high HbA1c was associated with high frequency hearing impairment. In non-smokers, HbA1c ≥8.0% was associated with high frequency hearing impairment, with a multivariable hazard ratio (95% confidence interval) compared with HbA1c 5.0-5.4% of 1.46 (1.10-1.94) in men and 2.15 (1.13-4.10) in women. There was no significant association between HbA1c and hearing impairment in smokers. A J-shaped association between HbA1c and high frequency hearing impairment was observed for participants with diabetes at baseline. HbA1c was not associated with low frequency hearing impairment among any participants.

Conclusions HbA1c ≥8.0% of non-smokers and ≥7.3% of participants with diabetes was associated with high frequency hearing impairment. These findings indicate that appropriate glycemic control may prevent diabetic-related hearing impairment.

Strengths and limitations of this study

- This study included a large number of participants, accounting for gender and smoking status.
- To determine whether HbA1c was associated with hearing impairment among participants with diabetes at baseline.
- Information on ototoxic drug use, ear surgery, and ear infection was was not obtained.

BACKGROUND

Patients with hearing impairment experience a range of complications, including impaired quality of life, dementia, depression, loneliness, poor self-esteem and functional disability (1-4). These complications have made this condition a social and economic problem worldwide. More than 5% of the world population has hearing impairment, and this is expected to increase with the aging of the population (5). Although this bleak picture points to the importance of identifying preventable risk factors for hearing impairment, such studies are in fact scarce.

Emerging evidence suggests that diabetes mellitus may be a risk factor for hearing impairment. Meta-analyses of 13 cross-sectional studies showed that subjects with diabetes had a 2-fold-increased risk of developing hearing impairment (odds ratio 2.15, 95%CI 1.72-2.68) (6). Diabetic hearing impairment is hypothesized to be due to microvascular complications (7, 8). Diabetic hearing impairment may thus be prevented by appropriate glycemic control, which has been shown to be effective for other microvascular complications of diabetes, such as retinopathy, nephropathy and neuropathy (9-12). Three studies have reported the association between hearing impairment and hemoglobin A1c (HbA1c), an indicator for glycemic control (13-15). One of these reported a positive dose-relationship between HbA1c and hearing

impairment as defined using a pure-tone average threshold of mainly low frequencies (15), while the other two reported that HbA1c was positively associated with high frequency hearing impairment (13, 14). Nevertheless, no study has yet reported the precise shape of the dose-relationship between HbA1c and high frequency hearing impairment. Furthermore, no study has yet investigated whether HbA1c is associated with hearing impairment among those with diabetes.

In Japan, a pure-tone audiometric test is mandatory in annual occupational health check-ups (16). The large sample size this affords has enabled us to investigate the dose-response relationship between HbA1c and hearing impairment, while accounting for well-known risk factors of hearing impairment such as gender and smoking (17, 18).

The present study had two aims. The first aim was to investigate the association between HbA1c and the incidence of hearing impairment using a large dataset from annual occupational health check-ups in Japan, accounting for gender and smoking status. The second aim was to determine whether HbA1c was associated with hearing impairment among participants with diabetes.

METHODS

Study population

The present study was conducted using data from annual health check-ups of Japanese workers. The All Japan Labor Welfare Foundation, a health service provider with centers in Tokyo, Aomori, Nagano, Yamagata, Ibaraki, Gunma and Nagoya provided the data from April 2008 through Dec 2015, allowing a maximum of 7 years of follow-up. In Japan, annual health check-ups are mandatory for all employees and include a hearing test under the Industrial Safety and Health Act. Nearly all employees attend a health check-up every year. Participants were mainly Japanese employees but also included a small number of their dependents, employers and foreign workers.

A total of 312,512 participants aged 30-65 years underwent a hearing test and HbA1c test at baseline (between Apr 2008 and Mar 2009). Of these, we excluded participants with hearing impairment at baseline (n=51,489). Given that diabetic patients with complications may receive more intensive treatments, which may bias the association between HbA1c and hearing impairment, we excluded participants with cardiovascular disease and stroke (n=913). We further excluded participants who did not attend any subsequent health examinations or hearing tests (n=48,618). After further exclusion of 8,517 participants with missing information on covariates (5,011 for smoking status, 5,152 for alcohol consumption, 1,815 for physical activity data, 5 for body mass index (BMI), 9 for hypertension and 9 for dyslipidemia data; some participants had missing

data for more than one parameter), leaving 202,975 participants (131,689 men and 71,286 women) for analysis.

Ethics

We obtained written informed consent from each participant who attended the heath check-up after April 2013. Before March 2013, we disclosed the purpose of our study by posters and the participants had the opportunity to refuse the use of their data for the study. This procedure conforms to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, where the obtaining consent may be simplified for observational studies using existing data. The research protocol including consent procedure was approved by the Ethics Committee of the Faculty of Medicine, Toho University (No. 25017 and No.A16130) and the Ethics Committee of the National Center for Global Health and Medicine (No. NCGM-G-001254-02).

Ascertainment of hearing impairment

Trained staff performed pure-tone air-conduction audiometry using an audiometer (AA-57, RION Inc., Tokyo, Japan). Low frequency hearing impairment was defined as failure to hear a pure-tone signal of 30dB at 1 kHz in the better ear, and high frequency hearing impairment as failure to hear a pure-tone signal of 40dB at 4 kHz in the better ear. These thresholds are recommended for use in annual health check-ups by Ministry

of Health, Labor and Welfare in Japan (16). Onset of hearing impairment was defined as the day of the health check-up on which hearing impairment was first detected.

Data collection and measurements at baseline (between Apr 2008 and Mar 2009)

We used a self-administered questionnaire developed by the Ministry of Health, Labor and Welfare for a specific health examination, namely the national health checkup system focused on metabolic syndrome (19), to assess medical history, regular physical activity (walking time <60 min/day or ≥60 min/day), smoking status (non-smoker, daily smoker ≤20 cigarettes/day or >20 cigarettes/day), alcohol consumption (non-drinker, <1 *go*, 1 to <2 *go* or ≥2 *go*/day; one *go* of sake, a traditional Japanese beverage, is equal to about 180 mL of 10-14% ethanol and contains about 23 g of ethanol) (20), and self-reported diabetes (treatments with anti-diabetic medication or a self-reported history of diabetes: yes or no). Job type was categorized as professional job, management, office job, sales, service, telegraph, manufacturing, transportation and other. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in metres and categorized into 4 groups (<18.5, 18.5-22.9, 23-29.9, ≥30kg/m²). Blood pressure was measured in the sitting position using an automated sphygmomanometer (HEM-907, Omron, Kyoto, Japan). Participants with high blood

pressure (≥130 mmHg systolic or ≥85 mmHg diastolic) received a second measurement and the average was used for the analysis. Hypertension was defined by ≥140 mmHg systolic, ≥90 mmHg diastolic or the use of medication for hypertension. A venous blood sample was collected and stored in a cooler at 4 °C for transportation to an external laboratory (SRL, Tokyo, Japan). Triglyceride level was measured using an enzymatic colorimetric test and high-density lipoprotein cholesterol (HDL-C) was determined using a direct method. Dyslipidemia was defined by triglyceride ≥150 mg/dL (1.7 mmol/L) in men and women, HDL-C <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or use of medication for dyslipidemia. HbA1c was measured by latex agglutination turbidimetry and converted to the National Glycohemoglobin Standardization Program equivalent value (%) using the formula below, according to the Japan Diabetes Society statement (21) :

HbA1c (%) = 1.02 ×HbA1c (Japan Diabetes Society) (%) + 0.25%

Diabetes was defined as FPG≥126mg/dL, HbA1c≥6.5%, or self-reported diabetes.

Statistical analysis

Participants were divided into 7 groups according to their HbA1c level at baseline [<5.0% (31mmol/mol), 5.0-5.4% (31-36mmol/mol), 5.5-5.9% (37-41mmol/mol), 6.0-6.4% (42-46mmol/mol), 6.5-6.9% (48-52mmol/mol), 7.0-7.9% (53-63mmol/mol),

≥8.0% (64 mmol/mol)]. The HbA1c group specific baseline characteristics of participants were described as means (SD) for continuous variables and percentages for categorical variables. Person-years was calculated from baseline to the onset of hearing impairment, or the date of the last health check-up through Dec 2015 (whichever occurred first). Crude incident rates of hearing impairment were shown in events per 1000 person-years. Survival analyses were performed using Cox regression to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the incidence of hearing impairment across HbA1c categories, with 5.0-5.4% (31-36mmol/mol) as the reference value. The analyses were stratified by sex because the interaction between hearing impairments and sex was significant (p for interaction <0.001). Age-adjusted model (model 1) and multiple-adjusted model (model 2), which included alcohol consumption, physical activity, BMI, hypertension, dyslipidemia, self-reported diabetes and smoking status were used for the analysis. Although smoking status itself was related to hearing impairment in this study, the association between HbA1c and hearing impairment differed according to smoking status (p for interaction <0.001). We therefore additionally performed analyses according to combined HbA1c (7 groups) and smoking status (non-smoker and current smoker), by considering HbA1c 5.0-5.4% (31-36mmol/mol) and non-smoker as the reference category. We did not analyze

women's smokers because of the small number of cases. To assess whether control of HbA1c would reduce the incidence of hearing impairment in those with diabetes, we elucidated the shape of the relationship between HbA1c and high frequency hearing impairment among those with diabetes. We fitted restricted cubic splines models with seven knots placed at the 1th, 5th, 25th, 50th, 75th, 95th, and 99th centiles as reference values of HbA1c 6.6% (25th) (22). The HRs were adjusted for alcohol consumption, physical activity, BMI, hypertension, dyslipidemia and smoking status. As a sensitivity analysis, we further adjusted for job type in the main analyses (model 2) among participants with this information (n=126,823). We tested the proportional hazards assumption using Schoenfeld residuals. We found no significant deviations for any covariate. P value of two-tailed test <0.05 was considered statistically significant. Trend association was assessed by assigning ordinal numbers (0–6) to the HbA1c categories. We calculated the p for the quadratic trend because it was a better fit for the data than the simple linear model. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas, USA).

RESULTS

Baseline characteristics by category of HbA1c are shown in Table 1. The mean age of participants was 45 years for men and 47 years for women. Participants who had higher HbA1c tended to be non-drinkers and to have higher BMI, hypertension, and dyslipidemia in both men and women. Male participants with higher HbA1c tended to be smokers consuming > 20 cigarettes per day.

In men, 4,621 developed high frequency hearing impairment with 661,937 person-years (mean duration of follow-up was 5.0 years) and 1,311 developed low frequency hearing impairment with 670,153 person-years (5.1 years). In women, 582 developed high frequency hearing impairment with 345,312 person-years (4.8 years) and 1,207 developed low frequency hearing impairment with 344,057 person-years (4.8 years).

Table 2 shows the association between HbA1c and the incidence of hearing impairment. In the multivariable-adjusted model, HbA1c showed a quadratic trend with the incidence of high frequency hearing impairment in men (p for quadratic=0.007), and a statistically marginal association in women (p for quadratic=0.08). HbA1c was not associated with low frequency hearing impairment. Figure 1 shows the association between HbA1c and high frequency hearing impairment with accounting for smoking status [the interaction between HbA1c and smoking status (p for interaction <0.001)]. Compared to non-smokers with HbA1c 5.0-5.4% (31-36mmol/mol), non-smokers with

HbA1c ≥8.0% (64 mmol/mol) showed an association with hearing impairment [HR (95%CI) of 1.46 (1.11-1.92) in men and 2.36 (1.34-4.15) in women]. Although smokers had higher HRs of hearing impairment than non-smokers, HbA1c level was not associated with hearing impairment among smokers. Additional adjustments for job type did not affect the results (Appendix 1).

Figure 2 shows the spline regression model of high frequency hearing impairment at various HbA1c levels against a reference HbA1c level of 6.6% in participants with diabetes at baseline (n=10,154). The relationship between HbA1c and the incidence of hearing impairment was J-shaped, with the significant increase of HR for HbA1c≥7.2%.

DISCUSSION

In this study, we found a quadratic trend between HbA1c and the incidence of high frequency hearing impairment. In particular, HbA1c concentrations over 8.0% (64 mmol/mol) were associated with high frequency hearing impairment among non-smokers. A J-shaped association between HbA1c and high frequency hearing impairment was observed among participants with diabetes at baseline. Our findings indicate that appropriate glycemic control may prevent the incidence of diabetic hearing impairment.

Our finding of a quadratic trend between HbA1c and hearing impairment is supported by the results of two longitudinal studies. (13, 15) One of these reported an odds ratio (95% CI) of high frequency hearing impairment per 1.0% increase in HbA1c of 1.52 (1.03 to 2.23), albeit no statistical association between the three categories of HbA1c and high frequency hearing impairment (13). The second reported that HbA1c was positively associated with average hearing threshold, mainly among low frequencies (15). The present study provides novel evidence that an HbA1c of 8.0% (64 mmol/mol) or above is associated with increased risk of high frequency hearing impairment in non-smokers. Our findings are consistent with the work of Cruickshanks et al., who reported that poor glycemic control, defined by a glycosylated hemoglobin level, was associated with hearing impairment (23).

Additionally, we found that the J-shaped association between HbA1c and hearing impairment remained even among participants with diabetes at baseline. This result suggests that proper glycemic control may prevent diabetic-related hearing impairment even in those with diabetes. Previous studies have also reported a J-shaped association between HbA1c and diabetics complications, and noted that hypoglycemia might increase diabetic complications (24-26). More research is needed to determine a suitable

HbA1c level for glycemic targeting to prevent hearing impairment in diabetic management.

We found that high frequency hearing impairment has a quadratic trend with HbA1c among non-smokers but not smokers. Previous studies have reported an adverse effect of smoking cigarettes on hearing impairment (23, 27, 28). It is plausible that the effect of smoking cigarettes may be stronger than HbA1c and might mask the effect of HbA1c. Further research is needed to confirm the joint effect of smoking and HbA1c on hearing impairment.

The pathophysiology underlying high-HbA1c-associated hearing impairment is unclear, which allows for speculation. One possible explanation is that hyperglycemia-related microvascular complications lead to thickening of the cochlea and vestibulopathy, and result in hearing impairment (7, 8, 29-33). Diabetic-related hearing impairment has been mainly observed at high frequencies, suggesting that high frequency-specific areas of the cochlea may be more fragile to ischemic changes due to microvascular complications (34-38). This mechanism is supported by the J-shaped association between HbA1c and hearing impairment observed in the present study, since previous studies also reported a J-shaped-association between HbA1c and diabetic vascular complications (39, 40). Further studies to confirm this idea are required.

This study has several strengths. The large dataset allowed us to investigate the association between HbA1c and hearing impairment with comprehensive adjustment for covariates, and additionally, among participants with diabetes at baseline. Audiometry to confirm hearing impairment was conducted by trained staff. Several limitations of the study also need to be considered. First, information on noise exposure was not available and thus noise information was not considered in the analyses. However, a previous study reported that the relationship between diabetes and hearing impairment was independent of this variable (37). Moreover, in the present study, HbA1c level was associated with hearing impairment even after accounting for job type in a sensitivity analysis. Second, information on ototoxic drug use, ear surgery, and ear infection was not collected, and we were therefore unable to exclude cases of hearing impairment due to these factors. Third, blood pressure was measured once, followed by a second measurement if the first systolic blood pressure ≥130 mmHg systolic or diastolic blood pressure ≥85 mmHg. All participants didn't have the same evaluation of blood pressure. This may lead to misclassification of hypertension. Fourth, we did not account for gender or smoking status in the association between HbA1c and hearing impairment for participants with diabetes because of the small sample size. Fifth, the hearing test was only conducted at 1 kHz and 4 kHz. Hearing impairment at other frequencies could not

therefore be identified. Sixth, we cannot exclude the possibility of residual confounding and confounding by unmeasured variables. Finally, the study participants were mainly workers, and thus caution is required when generalizing our findings.

CONCLUSION

We found the quadratic trend between HbA1c and the incidence of high frequency hearing impairment in non-smokers. The trend between HbA1c and hearing impairment remained even among those with diabetes. These findings indicate that diabetic-related hearing impairment may be prevented with appropriate glycemic control. These findings warrant confirmation in interventional studies.

Abbreviations

HbA1c: hemoglobin A1c; BMI: body mass index; HR: hazard ratio; CI: confidence interval

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Contributors

SN, TaM and IK designed study and drafted the manuscript. SN, HHH, KaK, AN and KeK performed the data analysis. MD collected and interpreted the data. All authors

participated in interpretation of the findings, revised the paper critically for important intellectual content and approved the final version to be published. YN and YM provided administrative, technical and material support. SN and YN are guarantors.

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Competing interests

None declared. SN is occupational physicians in the participating company.

Ethics approval

The research protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University and the Ethics Committee of the National Center for Global Health and Medicine.

Patient and public involvement

No patient were involved in setting the research question or the outcome measures, planning for the design of the study. Detail has been removed from this case description/these case descriptions to ensure anonymity. Patient consent was not required for the study.

Data sharing statement

No additional data are available.

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Table 1 Baseline characteristics of study participants according to HbA_{1c} (n=202,975).

		HbA_{1c} (%) (mmol/mol)						
	Overall	<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)
Men								
n	131,689	10,701	53,839	50,957	8,995	2,488	2,224	2,485
Age (years)*	44.6 (9.1)	40.9 (8.2)	42.6 (8.6)	45.7 (9.0)	49.6 (8.6)	51.7 (7.9)	51.6 (7.8)	49.2 (8.2)
Walking time, ≥60 min/day (%)	16	16	17	17	15	15	16	13
Smoking status (%)								
Non-smoker	45.15	44	44	46	47	50	46	40
Daily consuming ≤20 cigarettes/day	37.04	39	39	36	34	31	32	35
Daily consuming >20 cigarettes/day	17.8	17	17	18	19	19	22	25
Alcohol consumption (%)								
Non-drinker	26	19	24	29	31	30	33	36
Drinker <1 *go*/day†	35	32	35	36	34	34	30	32
Drinker 1 to <2 *go*/day†	26	30	27	25	25	25	26	22
Drinker ≥2 *go*/day†	12	19	13	10	10	11	11	10
Self-reported diabetes (%)‡	2.3	0.07	0.10	0.4	4.6	22.4	41.1	37.3
BMI (kg/m2)*	23.8 (3.5)	22.6 (2.9)	23.2 (3.1)	24.0 (3.5)	25.4 (4.0)	26.0 (4.2)	26.3 (4.3)	26.4 (4.5)
Hypertension (%)§	28	21	22	29	44	57	57	53
Dyslipidemia (%)ǁ	39	29	33	41	54	59	60	65
Women								
n	71,286	5,880	28,277	29,741	5,286	890	618	594
Age (years)*	47.1 (9.0)	41.5 (7.6)	44.6 (8.6)	49.0 (8.6)	52.6 (7.6)	53.9 (7.2)	53.9 (7.2)	52.0 (7.6)
Walking time, ≥60 min/day (%)	12	11	11	12	13	12	13	11
Smoking status (%)								
Non-smoker	80	71	77	83	86	86	83	77
Daily consuming ≤20 cigarettes/day	19	26	21	16	13	13	16	22
Daily consuming >20 cigarettes/day	1.4	2.5	1.5	1.2	1.2	1.1	1.5	1.9
Alcohol consumption (%)								
Non-drinker	60	45	56	65	70	74	73	78
Drinker <1 *go*/day†	31	36	34	29	26	22	22	19
Drinker 1 to <2 *go*/day†	6.8	14.4	7.8	5.0	3.8	3.9	3.7	2.7
Drinker ≥2 *go*/day†	1.7	5.3	1.9	1.0	0.5	0.6	0.5	0.7
Self-reported diabetes (%)‡	1.2	0.05	0.03	0.1	2.5	17.4	38.2	47.5
BMI (kg/m2)*	22.3 (3.6)	21.2 (2.9)	21.6 (3.2)	22.5 (3.7)	23.9 (4.3)	25.5 (4.7)	26.4 (4.8)	26.6 (4.6)
Hypertension (%)§	19	11	14	21	34	52	59	53
Dyslipidemia (%)ǁ	22	13	16	24	39	54	61	59

Longitudinal survey of 202,950 examinees in All Japan Labor Welfare Foundation, Japan, 2008.

* Mean (SD)

† One *go* contains ~23g of ethanol.

‡ Self-reported diagnosis of diabetes or receiving medication.

§ Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication.

ǁ Triglyceride level ≥150mg/dL (1.7mmol/L), high-density lipoprotein cholesterol level <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mml/L) in women or receiving medication.

Table 2 Hazard ratio of hearing impairment according to baseline HbA_{1c} (n = 202,975).

		HbA_{1c} (%) (mmol/mol)							
		<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)	P for quadratic
Low frequency									
Men	Person-year	54,055	275,953	261,290	44,807	11,798	10,637	11,613	
	No. cases	84	447	548	122	45	26	39	
	Model 1	1.15 (0.91 to 1.45)	1.00	0.98 (0.86 to 1.11)	0.94 (0.77 to 1.15)	1.11 (0.81 to 1.51)	0.73 (0.49 to 1.08)	1.22 (0.88 to 1.70)	0.15
	Model 2	1.11 (0.88 to 1.40)	1.00	1.00 (0.88 to 1.14)	0.98 (0.79 to 1.20)	1.16 (0.84 to 1.60)	0.75 (0.49 to 1.15)	1.26 (0.88 to 1.80)	0.27
Women	Person-year	28,447	137,761	143,295	25,083	4,136	2,760	2,576	
	No. cases	65	415	553	133	18	14	9	
	Model 1	1.04 (0.80 to 1.35)	1.00	0.90 (0.79 to 1.03)	0.94 (0.77 to 1.14)	0.71 (0.44 to 1.14)	0.86 (0.51 to 1.48)	0.68 (0.35 to 1.31)	0.79
	Model 2	1.04 (0.80 to 1.35)	1.00	0.91 (0.80 to 1.03)	0.93 (0.76 to 1.14)	0.67 (0.41 to 1.10)	0.77 (0.43 to 1.38)	0.57 (0.28 to 1.19)	0.51
High frequency									
Men	Person-year	53,617	273,025	257,812	44,093	11,621	10,345	11,424	
	No. cases	280	1,610	1,941	416	116	128	130	
	Model 1	1.05 (0.92 to 1.19)	1.00	0.98 (0.91 to 1.04)	0.91 (0.82 to 1.02)	0.82 (0.67 to 0.99)	1.05 (0.88 to 1.26)	1.15 (0.96 to 1.38)	0.003
	Model 2	1.03 (0.90 to 1.17)	1.00	0.99 (0.92 to 1.06)	0.93 (0.83 to 1.03)	0.84 (0.69 to 1.02)	1.08 (0.89 to 1.32)	1.18 (0.97 to 1.43)	0.007
Women	Person-year	28,520	138,232	143,882	25,246	4,124	2,753	2,555	
	No. cases	23	169	277	67	18	13	15	
	Model 1	1.02 (0.66 to 1.58)	1.00	1.00 (0.83 to 1.22)	0.97 (0.73 to 1.29)	1.43 (0.88 to 2.34)	1.62 (0.92 to 2.86)	2.41 (1.42 to 4.10)	0.03
	Model 2	1.03 (0.66 to 1.60)	1.00	0.97 (0.80 to 1.17)	0.86 (0.64 to 1.16)	1.17 (0.70 to 1.95)	1.24 (0.67 to 2.29)	1.78 (0.95 to 3.34)	0.08

Model 1: Adjusted for age.

Model 2: Adjusted for age, walking time, smoking status, alcohol consumption, self-reported diabetes, BMI, hypertension and hyperlipidemia.

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Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.
Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), self-reported diabetes, hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving medication).

Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5, p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), smoking status (non-smoker, smoker consuming ≤ 20, or > 20 cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

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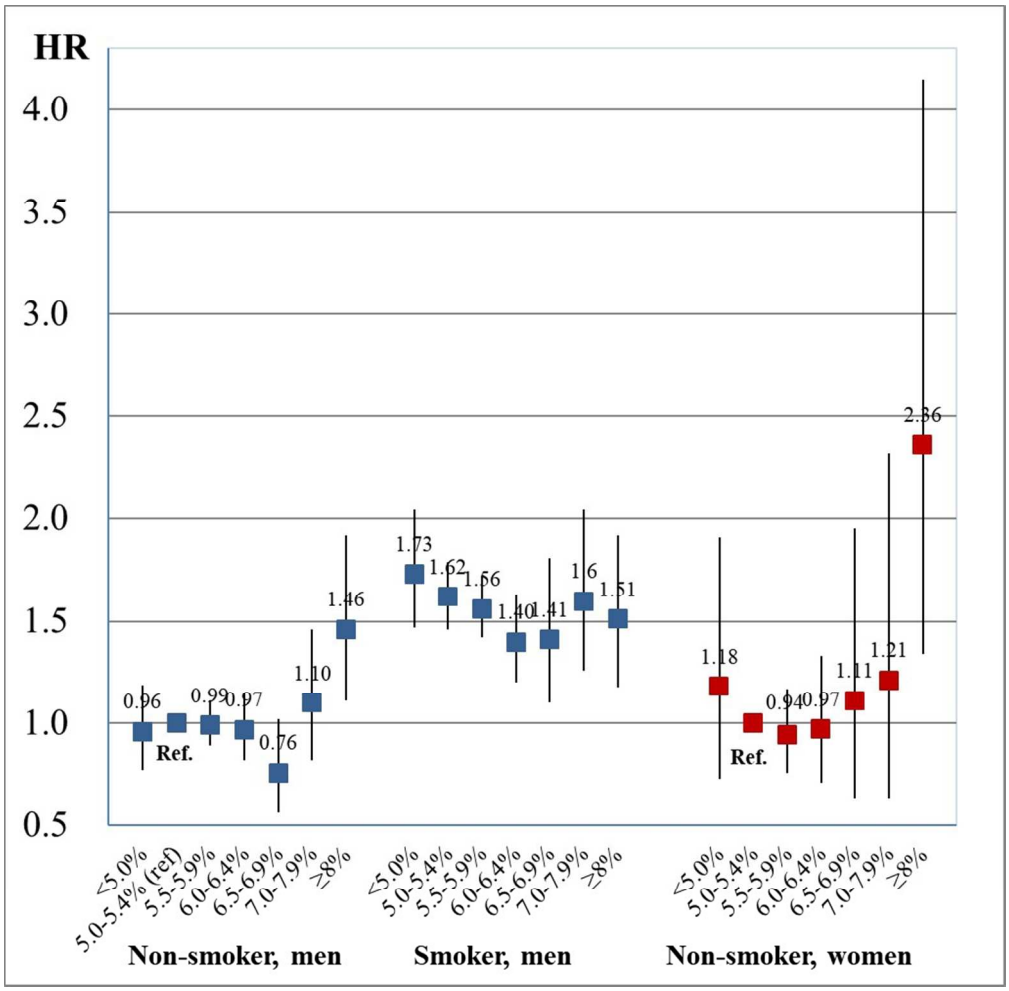

Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.

Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), self-reported diabetes, hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving medication).

270x265mm (96 x 96 DPI)

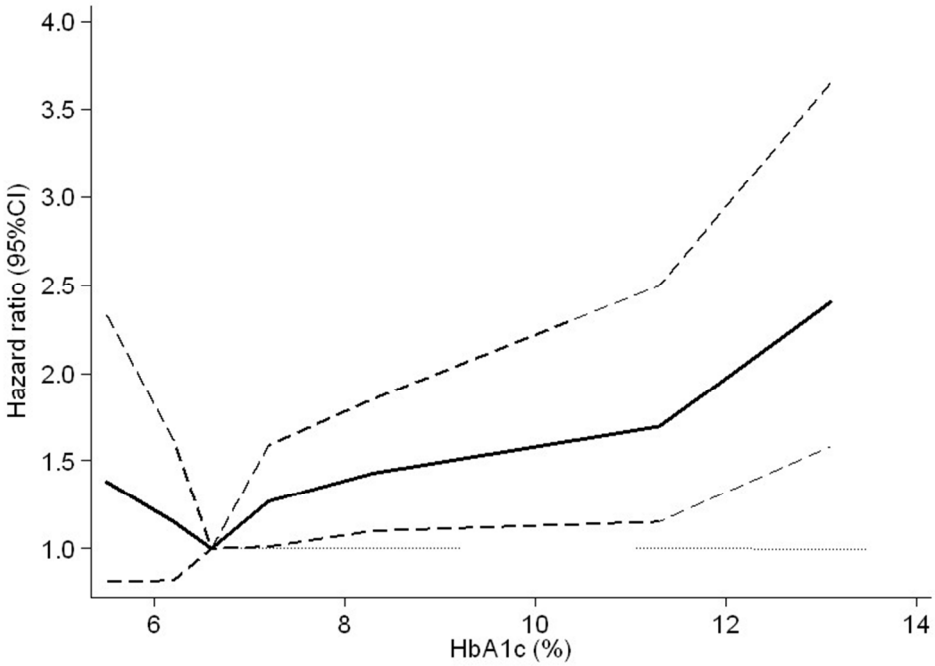

Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5, p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), smoking status (non-smoker, smoker consuming ≤ 20, or > 20 cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

222x162mm (96 x 96 DPI)

Appendix 1. The association between baseline HbA_{1c} and Incidence of high frequency hearing impairment (n=126,823).

		HbA_{1c} (%) (mmol/mol)							
		<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)	P for quadratic
Men	Person-year	44,265	227,740	215,647	36,368	9,184	8,148	8,888	
	No.cases	229	1,345	1,535	329	91	99	100	
	non-smoker	0.94 (0.73 to 1.20)	1.00	0.93 (0.82 to 1.05)	0.89 (0.73 to 1.07)	0.68 (0.48 to 0.96)	1.10 (0.80 to 1.53)	1.37 (1.00 to 1.88)	0.01
	smoker	1.06 (0.89 to 1.26)	1.00	0.95 (0.86 to 1.05)	0.91 (0.77 to 1.07)	1.00 (0.76 to 1.31)	1.10 (0.84 to 1.44)	1.04 (0.79 to 1.37)	0.23
Women	Person-year	22,749	110,979	114,327	19,601	3,143	2,062	1,813	
	No.cases	19	140	214	48	15	11	13	
	non-smoker	1.11 (0.65 to 1.91)	1.00	0.92 (0.72 to 1.18)	0.88 (0.61 to 1.26)	1.28 (0.69 to 2.35)	1.47 (0.73 to 2.94)	2.83 (1.53 to 5.24)	0.005

Adjusted for age, walking time, alcohol consumption, self-reported diabetes, BMI, hypertension, hyperlipidemia and job type.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 Line1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P3 Line31, P4 Line51
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P5 Line64-79
Objectives	3	State specific objectives, including any prespecified hypotheses	P6 Line83-88
Methods			
Study design	4	Present key elements of study design early in the paper	P7 Line90
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P7 Line90-107
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P7 Line99-108
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P8 Line118-155
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	P9 Line143-153
Bias	9	Describe any efforts to address potential sources of bias	P15 Line271-278, Line282
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P9 Line127-143
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P10 Line157-193
		(*b*) Describe any methods used to examine subgroups and interactions	P11 Line173-

	184
(*c*) Explain how missing data were addressed	P7 Line105-107
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	P12 Line185-187

Continued on next page

Results			
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	Table1,2, Fig2
		(b) Give reasons for non-participation at each stage	P11 Line178
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P12 Line196-200, Table1
		(b) Indicate number of participants with missing data for each variable of interest	P7 Line1001-109
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	P12 Line201-206
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	P12 Line200-206
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	P13 Line215
		(*b*) Report category boundaries when continuous variables were categorized	P10 Line158-161
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P14 Line218-223
Discussion			
Key results	18	Summarise key results with reference to study objectives	P14 Line225-231
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	P17 Line271-284
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P17 Line285-290
Generalisability	21	Discuss the generalisability (external validity) of the study results	P17 Line284-

			285
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	P18 Line301

*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.

BMJ Open

Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large occupational health check-up data of Japan

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Secondary Subject Heading:	Diabetes and endocrinology, Ear, nose and throat/otolaryngology, Epidemiology
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Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large occupational health check-up data of Japan

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Word count 3,091

Tables 2

Figures 2

Objectives The aim of this study was to determine whether hemoglobin A1c (HbA1c) level is associated with the incidence of hearing impairment accounting for smoking status and diabetic condition at baseline.

Methods Participants were 131,689 men and 71,286 women aged 30-65 years and free of hearing impairment at baseline (2008) who attended annual health check-ups from 2008 to 2015. We defined low frequency hearing impairment at a hearing threshold >30 dB at 1 kHz and high frequency at >40 dB at 4 kHz in the better ear in pure-tone audiometric tests. HbA1c was categorized into 7 categories. The association between HbA1c and hearing impairment was assessed using the Cox proportional hazards model.

Results On 5 years' mean follow-up, high HbA1c was associated with high frequency hearing impairment. In non-smokers, HbA1c ≥8.0% was associated with high frequency hearing impairment, with a multivariable hazard ratio (95% confidence interval) compared with HbA1c 5.0-5.4% of 1.46 (1.10-1.94) in men and 2.15 (1.13-4.10) in women. There was no significant association between HbA1c and hearing impairment in smokers. A J-shaped association between HbA1c and high frequency hearing impairment was observed for participants with diabetes at baseline. HbA1c was not associated with low frequency hearing impairment among any participants.

Conclusions HbA1c ≥8.0% of non-smokers and ≥7.3% of participants with diabetes was associated with high frequency hearing impairment. These findings indicate that appropriate glycemic control may prevent diabetic-related hearing impairment.

Strengths and limitations of this study

- This study included a large number of participants, accounting for gender and smoking status.
- To determine whether HbA1c was associated with hearing impairment among participants with diabetes at baseline.
- Information on noise exposure, ototoxic drug use, ear surgery, and ear infection was not obtained.

BACKGROUND

Patients with hearing impairment experience a range of complications, including impaired quality of life, dementia, depression, loneliness, poor self-esteem and functional disability (1-4). These complications have made this condition a social and economic problem worldwide. More than 5% of the world population has hearing impairment, and this is expected to increase with the aging of the population (5). Although this bleak picture points to the importance of identifying preventable risk factors for hearing impairment, such studies are in fact scarce.

Emerging evidence suggests that diabetes mellitus may be a risk factor for hearing impairment. Meta-analyses of 13 cross-sectional studies showed that subjects with diabetes had a 2-fold-increased risk of developing hearing impairment (odds ratio 2.15, 95%CI 1.72-2.68) (6). Diabetic hearing impairment is hypothesized to be due to microvascular complications (7, 8). Diabetic hearing impairment may thus be prevented by appropriate glycemic control, which has been shown to be effective for other microvascular complications of diabetes, such as retinopathy, nephropathy and neuropathy (9-12). Three studies have reported the association between hearing impairment and hemoglobin A1c (HbA1c), an indicator for glycemic control (13-15). One of these reported a positive dose-relationship between HbA1c and hearing

impairment as defined using a pure-tone average threshold of mainly low frequencies (15), while the other two reported that HbA1c was positively associated with high frequency hearing impairment (13, 14). Nevertheless, no study has yet reported the precise shape of the dose-relationship between HbA1c and high frequency hearing impairment. Furthermore, no study has yet investigated whether HbA1c is associated with hearing impairment among those with diabetes.

In Japan, a pure-tone audiometric test is mandatory in annual occupational health check-ups (16). The large sample size this affords has enabled us to investigate the dose-response relationship between HbA1c and hearing impairment, while accounting for well-known risk factors of hearing impairment such as gender and smoking (17, 18).

The present study had two aims. The first aim was to investigate the association between HbA1c and the incidence of hearing impairment using a large dataset from annual occupational health check-ups in Japan, accounting for gender and smoking status. The second aim was to determine whether HbA1c was associated with hearing impairment among participants with diabetes.

METHODS

Study population

The present study was conducted using data from annual health check-ups of Japanese workers. The All Japan Labor Welfare Foundation, a health service provider with centers in Tokyo, Aomori, Nagano, Yamagata, Ibaraki, Gunma and Nagoya provided the data from April 2008 through Dec 2015, allowing a maximum of 7 years of follow-up. In Japan, annual health check-ups are mandatory for all employees and include a hearing test under the Industrial Safety and Health Act. Nearly all employees attend a health check-up every year. Participants were mainly Japanese employees but also included a small number of their dependents, employers and foreign workers.

A total of 312,512 participants aged 30-65 years underwent a hearing test and HbA1c test at baseline (between Apr 2008 and Mar 2009). Of these, we excluded participants with hearing impairment at baseline (n=51,489). Given that diabetic patients with complications may receive more intensive treatments, which may bias the association between HbA1c and hearing impairment, we excluded participants with cardiovascular disease and stroke (n=913). We further excluded participants who did not attend any subsequent health examinations or hearing tests (n=48,618). After further exclusion of 8,517 participants with missing information on covariates (5,011 for smoking status, 5,152 for alcohol consumption, 1,815 for physical activity data, 5 for body mass index (BMI), 9 for hypertension and 9 for dyslipidemia data; some participants had missing

data for more than one parameter), leaving 202,975 participants (131,689 men and 71,286 women) for analysis.

Ethics

We obtained written informed consent from each participant who attended the heath check-up after April 2013. Before March 2013, we disclosed the purpose of our study by posters and the participants had the opportunity to refuse the use of their data for the study. This procedure conforms to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, where the obtaining consent may be simplified for observational studies using existing data. The research protocol including consent procedure was approved by the Ethics Committee of the Faculty of Medicine, Toho University (No. 25017 and No.A16130) and the Ethics Committee of the National Center for Global Health and Medicine (No. NCGM-G-001254-02).

Ascertainment of hearing impairment

Trained staff performed pure-tone air-conduction audiometry using an audiometer (AA-57, RION Inc., Tokyo, Japan). Low frequency hearing impairment was defined as failure to hear a pure-tone signal of 30dB at 1 kHz in the better ear, and high frequency hearing impairment as failure to hear a pure-tone signal of 40dB at 4 kHz in the better ear. These thresholds are recommended for use in annual health check-ups by Ministry

of Health, Labor and Welfare in Japan (16). Onset of hearing impairment was defined as the day of the health check-up on which hearing impairment was first detected.

Data collection and measurements at baseline (between Apr 2008 and Mar 2009)

We used a self-administered questionnaire developed by the Ministry of Health, Labor and Welfare for a specific health examination, namely the national health checkup system focused on metabolic syndrome (19), to assess medical history, regular physical activity (walking time <60 min/day or ≥60 min/day), smoking status (non-smoker, daily smoker ≤20 cigarettes/day or >20 cigarettes/day), alcohol consumption (non-drinker, <1 *go*, 1 to <2 *go* or ≥2 *go*/day; one *go* of sake, a traditional Japanese beverage, is equal to about 180 mL of 10-14% ethanol and contains about 23 g of ethanol) (20), and self-reported diabetes (treatments with anti-diabetic medication or a self-reported history of diabetes: yes or no). Job type was categorized as professional job, management, office job, sales, service, telegraph, manufacturing, transportation and other. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in metres and categorized into 4 groups (<18.5, 18.5-22.9, 23-29.9, ≥30kg/m²). Blood pressure was measured in the sitting position using an automated sphygmomanometer (HEM-907, Omron, Kyoto, Japan). Participants with high blood

pressure (≥130 mmHg systolic or ≥85 mmHg diastolic) received a second measurement and the average was used for the analysis. Hypertension was defined by ≥140 mmHg systolic, ≥90 mmHg diastolic or the use of medication for hypertension. A venous blood sample was collected and stored in a cooler at 4 °C for transportation to an external laboratory (SRL, Tokyo, Japan). Triglyceride level was measured using an enzymatic colorimetric test and high-density lipoprotein cholesterol (HDL-C) was determined using a direct method. Dyslipidemia was defined by triglyceride ≥150 mg/dL (1.7 mmol/L) in men and women, HDL-C <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or use of medication for dyslipidemia. HbA1c was measured by latex agglutination turbidimetry and converted to the National Glycohemoglobin Standardization Program equivalent value (%) using the formula below, according to the Japan Diabetes Society statement (21) :

HbA1c (%) = 1.02 ×HbA1c (Japan Diabetes Society) (%) + 0.25%

Diabetes was defined as FPG≥126mg/dL, HbA1c≥6.5%, or self-reported diabetes.

Statistical analysis

Participants were divided into 7 groups according to their HbA1c level at baseline [<5.0% (31mmol/mol), 5.0-5.4% (31-36mmol/mol), 5.5-5.9% (37-41mmol/mol), 6.0-6.4% (42-46mmol/mol), 6.5-6.9% (48-52mmol/mol), 7.0-7.9% (53-63mmol/mol),

≥8.0% (64 mmol/mol)]. The HbA1c group specific baseline characteristics of participants were described as means (SD) for continuous variables and percentages for categorical variables. Person-years was calculated from baseline to the onset of hearing impairment, or the date of the last health check-up through Dec 2015 (whichever occurred first). Crude incident rates of hearing impairment were shown in events per 1000 person-years. Survival analyses were performed using Cox regression to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the incidence of hearing impairment across HbA1c categories, with 5.0-5.4% (31-36mmol/mol) as the reference value. The analyses were stratified by sex because the interaction between hearing impairments and sex was significant (p for interaction <0.001). Age-adjusted model (model 1) and multiple-adjusted model (model 2), which included alcohol consumption, physical activity, BMI, hypertension, dyslipidemia, self-reported diabetes and smoking status were used for the analysis. Although smoking status itself was related to hearing impairment in this study, the association between HbA1c and hearing impairment differed according to smoking status (p for interaction <0.001). We therefore additionally performed analyses according to combined HbA1c (7 groups) and smoking status (non-smoker and current smoker), by considering HbA1c 5.0-5.4% (31-36mmol/mol) and non-smoker as the reference category. We did not analyze

women's smokers because of the small number of cases. To assess whether control of HbA1c would reduce the incidence of hearing impairment in those with diabetes, we elucidated the shape of the relationship between HbA1c and high frequency hearing impairment among those with diabetes. We fitted restricted cubic splines models with seven knots placed at the 1th, 5th, 25th, 50th, 75th, 95th, and 99th centiles as reference values of HbA1c 6.6% (25th) (22). The HRs were adjusted for alcohol consumption, physical activity, BMI, hypertension, dyslipidemia and smoking status. As a sensitivity analysis, we further adjusted for job type in the main analyses (model 2) among participants with this information (n=126,823). We tested the proportional hazards assumption using Schoenfeld residuals. We found no significant deviations for any covariate. P value of two-tailed test <0.05 was considered statistically significant. Trend association was assessed by assigning ordinal numbers (0–6) to the HbA1c categories. We calculated the p for the quadratic trend because it was a better fit for the data than the simple linear model. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas, USA).

RESULTS

Baseline characteristics by category of HbA1c are shown in Table 1. The mean age of participants was 45 years for men and 47 years for women. Participants who had higher HbA1c tended to be non-drinkers and to have higher BMI, hypertension, and dyslipidemia in both men and women. Male participants with higher HbA1c tended to be smokers consuming > 20 cigarettes per day.

In men, 4,621 developed high frequency hearing impairment with 661,937 person-years (mean duration of follow-up was 5.0 years) and 1,311 developed low frequency hearing impairment with 670,153 person-years (5.1 years). In women, 582 developed high frequency hearing impairment with 345,312 person-years (4.8 years) and 1,207 developed low frequency hearing impairment with 344,057 person-years (4.8 years).

Table 2 shows the association between HbA1c and the incidence of hearing impairment. In the multivariable-adjusted model, HbA1c showed a quadratic trend with the incidence of high frequency hearing impairment in men (p for quadratic=0.007), and a statistically marginal association in women (p for quadratic=0.08). HbA1c was not associated with low frequency hearing impairment. Figure 1 shows the association between HbA1c and high frequency hearing impairment with accounting for smoking status [the interaction between HbA1c and smoking status (p for interaction <0.001)]. Compared to non-smokers with HbA1c 5.0-5.4% (31-36mmol/mol), non-smokers with

HbA1c ≥8.0% (64 mmol/mol) showed an association with hearing impairment [HR (95%CI) of 1.46 (1.11-1.92) in men and 2.36 (1.34-4.15) in women]. Although smokers had higher HRs of hearing impairment than non-smokers, HbA1c level was not associated with hearing impairment among smokers. Additional adjustments for job type did not affect the results (Appendix 1).

Figure 2 shows the spline regression model of high frequency hearing impairment at various HbA1c levels against a reference HbA1c level of 6.6% in participants with diabetes at baseline (n=10,154). The relationship between HbA1c and the incidence of hearing impairment was J-shaped, with the significant increase of HR for HbA1c≥7.2%.

DISCUSSION

In this study, we found a quadratic trend between HbA1c and the incidence of high frequency hearing impairment. In particular, HbA1c concentrations over 8.0% (64 mmol/mol) were associated with high frequency hearing impairment among non-smokers. A J-shaped association between HbA1c and high frequency hearing impairment was observed among participants with diabetes at baseline. Our findings indicate that appropriate glycemic control may prevent the incidence of diabetic hearing impairment.

Our finding of a quadratic trend between HbA1c and hearing impairment is supported by the results of two longitudinal studies. (13, 15) One of these reported an odds ratio (95% CI) of high frequency hearing impairment per 1.0% increase in HbA1c of 1.52 (1.03 to 2.23), albeit no statistical association between the three categories of HbA1c and high frequency hearing impairment (13). The second reported that HbA1c was positively associated with average hearing threshold, mainly among low frequencies (15). The present study provides novel evidence that an HbA1c of 8.0% (64 mmol/mol) or above is associated with increased risk of high frequency hearing impairment in non-smokers. Our findings are consistent with the work of Cruickshanks et al., who reported that poor glycemic control, defined by a glycosylated hemoglobin level, was associated with hearing impairment (23).

Additionally, we found that the J-shaped association between HbA1c and hearing impairment remained even among participants with diabetes at baseline. This result suggests that proper glycemic control may prevent diabetic-related hearing impairment even in those with diabetes. Previous studies have also reported a J-shaped association between HbA1c and diabetics complications, and noted that hypoglycemia might increase diabetic complications (24-26). More research is needed to determine a

suitable HbA1c level for glycemic targeting to prevent hearing impairment in diabetic management.

We found that high frequency hearing impairment has a quadratic trend with HbA1c among non-smokers but not smokers. Previous studies have reported an adverse effect of smoking cigarettes on hearing impairment (23, 27, 28). It is plausible that the effect of smoking cigarettes may be stronger than HbA1c and might mask the effect of HbA1c. Further research is needed to confirm the joint effect of smoking and HbA1c on hearing impairment.

The pathophysiology underlying high-HbA1c-associated hearing impairment is unclear, which allows for speculation. One possible explanation is that hyperglycemia-related microvascular complications lead to thickening of the cochlea and vestibulopathy, and result in hearing impairment (7, 8, 29-33). Diabetic-related hearing impairment has been mainly observed at high frequencies, suggesting that high frequency-specific areas of the cochlea may be more fragile to ischemic changes due to microvascular complications (34-38). This mechanism is supported by the J-shaped association between HbA1c and hearing impairment observed in the present study, since previous studies also reported a J-shaped-association between HbA1c and diabetic vascular complications (39, 40). Further studies to confirm this idea are required.

This study has several strengths. The large dataset allowed us to investigate the association between HbA1c and hearing impairment with comprehensive adjustment for covariates, and additionally, among participants with diabetes at baseline. Audiometry to confirm hearing impairment was conducted by trained staff. Several limitations of the study also need to be considered. First, though noise exposure is an important risk factor on hearing impairment (41, 42), information on noise exposure was not available and thus noise information was not considered in the analyses. The present study thus might include the cofounding influence of noise exposure. However, a previous study reported that the relationship between diabetes and hearing impairment was independent of this variable (37). Moreover, in the present study, HbA1c level was associated with hearing impairment even after accounting for job type in a sensitivity analysis. Second, information on ototoxic drug use, ear surgery, and ear infection was not collected, and we were therefore unable to exclude cases of hearing impairment due to these factors. Third, blood pressure was measured once, followed by a second measurement if the first systolic blood pressure ≥130 mmHg systolic or diastolic blood pressure ≥85 mmHg. All participants didn't have the same evaluation of blood pressure. This may lead to misclassification of hypertension. Fourth, we did not account for gender or smoking status in the association between HbA1c and hearing impairment for participants with

diabetes because of the small sample size. Fifth, the hearing test was only conducted at 1 kHz and 4 kHz. Hearing impairment at other frequencies could not therefore be identified. Sixth, we cannot exclude the possibility of residual confounding and confounding by unmeasured variables. Finally, the study participants were mainly workers, and thus caution is required when generalizing our findings.

CONCLUSION

We found the quadratic trend between HbA1c and the incidence of high frequency hearing impairment in non-smokers. The trend between HbA1c and hearing impairment remained even among those with diabetes. These findings indicate that diabetic-related hearing impairment may be prevented with appropriate glycemic control. These findings warrant confirmation in interventional studies.

Abbreviations

HbA1c: hemoglobin A1c; BMI: body mass index; HR: hazard ratio; CI: confidence interval

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Contributors

SN, TaM and IK designed study and drafted the manuscript. SN, HHH, KaK, AN and KeK performed the data analysis. MD collected and interpreted the data. All authors participated in interpretation of the findings, revised the paper critically for important intellectual content and approved the final version to be published. YN and YM provided administrative, technical and material support. SN and YN are guarantors.

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Competing interests

None declared. SN is occupational physicians in the participating company.

Ethics approval

The research protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University and the Ethics Committee of the National Center for Global Health and Medicine.

Patient and public involvement

No patient were involved in setting the research question or the outcome measures, planning for the design of the study. Detail has been removed from this case description/these case descriptions to ensure anonymity. Patient consent was not required for the study.

Data sharing statement

No additional data are available.

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Table 1 Baseline characteristics of study participants according to HbA_{1c} (n=202,975).

		HbA_{1c} (%) (mmol/mol)						
	Overall	<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)
Men								
n	131,689	10,701	53,839	50,957	8,995	2,488	2,224	2,485
Age (years)*	44.6 (9.1)	40.9 (8.2)	42.6 (8.6)	45.7 (9.0)	49.6 (8.6)	51.7 (7.9)	51.6 (7.8)	49.2 (8.2)
Walking time, ≥60 min/day (%)	16	16	17	17	15	15	16	13
Smoking status (%)								
Non-smoker	45.15	44	44	46	47	50	46	40
Daily consuming ≤20 cigarettes/day	37.04	39	39	36	34	31	32	35
Daily consuming >20 cigarettes/day	17.8	17	17	18	19	19	22	25
Alcohol consumption (%)								
Non-drinker	26	19	24	29	31	30	33	36
Drinker <1 *go*/day†	35	32	35	36	34	34	30	32
Drinker 1 to <2 *go*/day†	26	30	27	25	25	25	26	22
Drinker ≥2 *go*/day†	12	19	13	10	10	11	11	10
Self-reported diabetes (%)‡	2.3	0.07	0.10	0.4	4.6	22.4	41.1	37.3
BMI (kg/m2)*	23.8 (3.5)	22.6 (2.9)	23.2 (3.1)	24.0 (3.5)	25.4 (4.0)	26.0 (4.2)	26.3 (4.3)	26.4 (4.5)
Hypertension (%)§	28	21	22	29	44	57	57	53
Dyslipidemia (%)ǀ	39	29	33	41	54	59	60	65
Women								
n	71,286	5,880	28,277	29,741	5,286	890	618	594
Age (years)*	47.1 (9.0)	41.5 (7.6)	44.6 (8.6)	49.0 (8.6)	52.6 (7.6)	53.9 (7.2)	53.9 (7.2)	52.0 (7.6)
Walking time, ≥60 min/day (%)	12	11	11	12	13	12	13	11
Smoking status (%)								
Non-smoker	80	71	77	83	86	86	83	77
Daily consuming ≤20 cigarettes/day	19	26	21	16	13	13	16	22
Daily consuming >20 cigarettes/day	1.4	2.5	1.5	1.2	1.2	1.1	1.5	1.9
Alcohol consumption (%)								
Non-drinker	60	45	56	65	70	74	73	78
Drinker <1 *go*/day†	31	36	34	29	26	22	22	19
Drinker 1 to <2 *go*/day†	6.8	14.4	7.8	5.0	3.8	3.9	3.7	2.7
Drinker ≥2 *go*/day†	1.7	5.3	1.9	1.0	0.5	0.6	0.5	0.7
Self-reported diabetes (%)‡	1.2	0.05	0.03	0.1	2.5	17.4	38.2	47.5
BMI (kg/m2)*	22.3 (3.6)	21.2 (2.9)	21.6 (3.2)	22.5 (3.7)	23.9 (4.3)	25.5 (4.7)	26.4 (4.8)	26.6 (4.6)
Hypertension (%)§	19	11	14	21	34	52	59	53
Dyslipidemia (%)ǀ	22	13	16	24	39	54	61	59

Longitudinal survey of 202,950 examinees in All Japan Labor Welfare Foundation, Japan, 2008.

* Mean (SD)

ǀ One *go* contains ~23g of ethanol.

‡ Self-reported diagnosis of diabetes or receiving medication.

§ Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication.

ǀ Triglyceride level ≥150mg/dL (1.7mmol/L), high-density lipoprotein cholesterol level <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mml/L) in women or receiving medication.

Table 2 Hazard ratio of hearing impairment according to baseline HbA_{1c} (n = 202,975).

		HbA_{1c} (%) (mmol/mol)							
		<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)	P for quadratic
Low frequency									
Men	Person-year	54,055	275,953	261,290	44,807	11,798	10,637	11,613	
	No. cases	84	447	548	122	45	26	39	
	Model 1	1.15 (0.91 to 1.45)	1.00	0.98 (0.86 to 1.11)	0.94 (0.77 to 1.15)	1.11 (0.81 to 1.51)	0.73 (0.49 to 1.08)	1.22 (0.88 to 1.70)	0.15
	Model 2	1.11 (0.88 to 1.40)	1.00	1.00 (0.88 to 1.14)	0.98 (0.79 to 1.20)	1.16 (0.84 to 1.60)	0.75 (0.49 to 1.15)	1.26 (0.88 to 1.80)	0.27
Women	Person-year	28,447	137,761	143,295	25,083	4,136	2,760	2,576	
	No. cases	65	415	553	133	18	14	9	
	Model 1	1.04 (0.80 to 1.35)	1.00	0.90 (0.79 to 1.03)	0.94 (0.77 to 1.14)	0.71 (0.44 to 1.14)	0.86 (0.51 to 1.48)	0.68 (0.35 to 1.31)	0.79
	Model 2	1.04 (0.80 to 1.35)	1.00	0.91 (0.80 to 1.03)	0.93 (0.76 to 1.14)	0.67 (0.41 to 1.10)	0.77 (0.43 to 1.38)	0.57 (0.28 to 1.19)	0.51
High frequency									
Men	Person-year	53,617	273,025	257,812	44,093	11,621	10,345	11,424	
	No. cases	280	1,610	1,941	416	116	128	130	
	Model 1	1.05 (0.92 to 1.19)	1.00	0.98 (0.91 to 1.04)	0.91 (0.82 to 1.02)	0.82 (0.67 to 0.99)	1.05 (0.88 to 1.26)	1.15 (0.96 to 1.38)	0.003
	Model 2	1.03 (0.90 to 1.17)	1.00	0.99 (0.92 to 1.06)	0.93 (0.83 to 1.03)	0.84 (0.69 to 1.02)	1.08 (0.89 to 1.32)	1.18 (0.97 to 1.43)	0.007
Women	Person-year	28,520	138,232	143,882	25,246	4,124	2,753	2,555	
	No. cases	23	169	277	67	18	13	15	
	Model 1	1.02 (0.66 to 1.58)	1.00	1.00 (0.83 to 1.22)	0.97 (0.73 to 1.29)	1.43 (0.88 to 2.34)	1.62 (0.92 to 2.86)	2.41 (1.42 to 4.10)	0.03
	Model 2	1.03 (0.66 to 1.60)	1.00	0.97 (0.80 to 1.17)	0.86 (0.64 to 1.16)	1.17 (0.70 to 1.95)	1.24 (0.67 to 2.29)	1.78 (0.95 to 3.34)	0.08

Model 1: Adjusted for age.

Model 2: Adjusted for age, walking time, smoking status, alcohol consumption, self-reported diabetes, BMI, hypertension and hyperlipidemia.

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Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.
Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), self-reported diabetes, hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving medication).

Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5, p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), smoking status (non-smoker, smoker consuming ≤ 20, or > 20 cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

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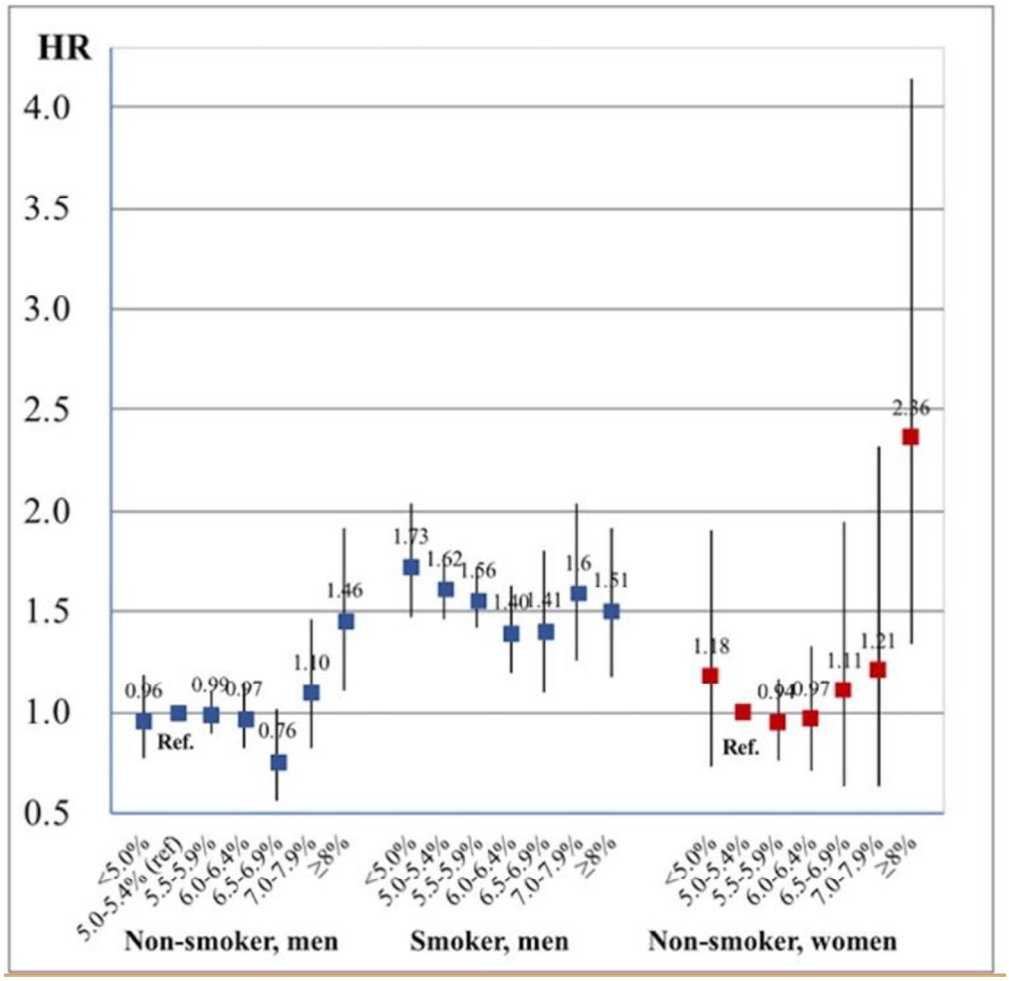

Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.

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203x197mm (96 x 96 DPI)

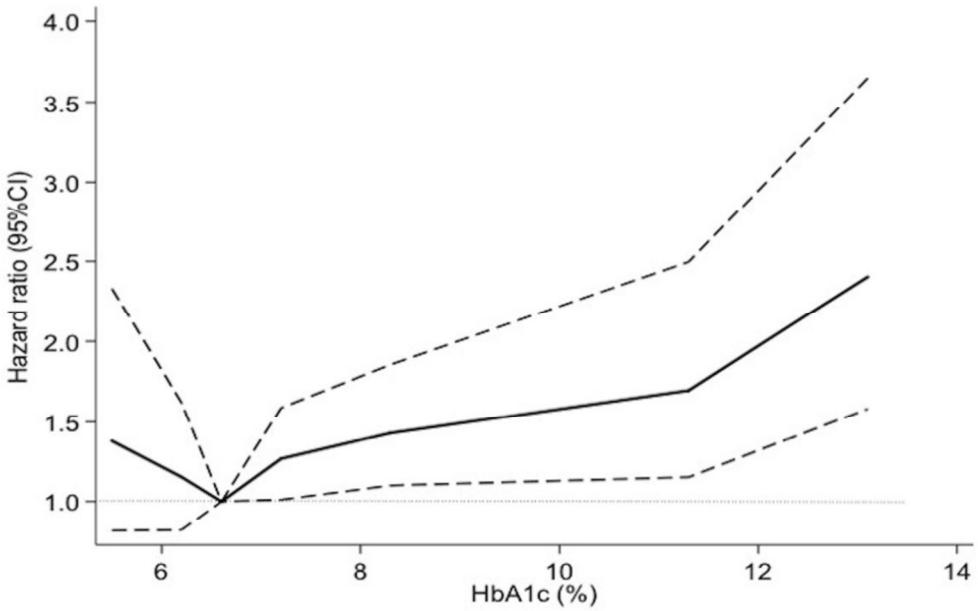

Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5, p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), smoking status (non-smoker, smoker consuming ≤ 20, or > 20 cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

312x193mm (96 x 96 DPI)

Appendix 1. The association between baseline HbA_{1c} and Incidence of high frequency hearing impairment (n=126,823).

		HbA_{1c} (%) (mmol/mol)							
		<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)	P for quadratic
Men	Person-year	44,265	227,740	215,647	36,368	9,184	8,148	8,888	
	No.cases	229	1,345	1,535	329	91	99	100	
	non-smoker	0.94 (0.73 to 1.20)	1.00	0.93 (0.82 to 1.05)	0.89 (0.73 to 1.07)	0.68 (0.48 to 0.96)	1.10 (0.80 to 1.53)	1.37 (1.00 to 1.88)	0.01
	smoker	1.06 (0.89 to 1.26)	1.00	0.95 (0.86 to 1.05)	0.91 (0.77 to 1.07)	1.00 (0.76 to 1.31)	1.10 (0.84 to 1.44)	1.04 (0.79 to 1.37)	0.23
Women	Person-year	22,749	110,979	114,327	19,601	3,143	2,062	1,813	
	No.cases	19	140	214	48	15	11	13	
	non-smoker	1.11 (0.65 to 1.91)	1.00	0.92 (0.72 to 1.18)	0.88 (0.61 to 1.26)	1.28 (0.69 to 2.35)	1.47 (0.73 to 2.94)	2.83 (1.53 to 5.24)	0.005

Adjusted for age, walking time, alcohol consumption, self-reported diabetes, BMI, hypertension, hyperlipidemia and job type.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 Line1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P3 Line31, P4 Line51
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P5 Line64-79
Objectives	3	State specific objectives, including any prespecified hypotheses	P6 Line83-88
Methods			
Study design	4	Present key elements of study design early in the paper	P7 Line90
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P7 Line90-107
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P7 Line99-108
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P8 Line118-155
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	P9 Line143-153
Bias	9	Describe any efforts to address potential sources of bias	P15 Line271-278, Line282
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P9 Line127-143
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P10 Line157-193
		(*b*) Describe any methods used to examine subgroups and interactions	P11 Line173-

	184
(*c*) Explain how missing data were addressed	P7 Line105-107
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	P12 Line185-187

Continued on next page

Results			
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	Table1,2, Fig2
		(b) Give reasons for non-participation at each stage	P11 Line178
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P12 Line196-200, Table1
		(b) Indicate number of participants with missing data for each variable of interest	P7 Line1001-109
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	P12 Line201-206
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	P12 Line200-206
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	P13 Line215
		(*b*) Report category boundaries when continuous variables were categorized	P10 Line158-161
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P14 Line218-223
Discussion			
Key results	18	Summarise key results with reference to study objectives	P14 Line225-231
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	P17 Line271-284
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P17 Line285-290
Generalisability	21	Discuss the generalisability (external validity) of the study results	P17 Line284-

			285
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	P18 Line301

*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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Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large occupational health check-up data of Japan

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Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large occupational health check-up data of Japan

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Word count 3,091

Tables 2

Figures 2

Objectives The aim of this study was to determine whether hemoglobin A1c (HbA1c) level is associated with the incidence of hearing impairment accounting for smoking status and diabetic condition at baseline.

Methods Participants were 131,689 men and 71,286 women aged 30-65 years and free of hearing impairment at baseline (2008) who attended Japanese occupational annual health check-ups from 2008 to 2015. We defined low frequency hearing impairment at a hearing threshold >30 dB at 1 kHz and high frequency at >40 dB at 4 kHz in the better ear in pure-tone audiometric tests. HbA1c was categorized into 7 categories. The association between HbA1c and hearing impairment was assessed using the Cox proportional hazards model.

Results On 5 years' mean follow-up, high HbA1c was associated with high frequency hearing impairment. In non-smokers, HbA1c ≥8.0% was associated with high frequency hearing impairment, with a multivariable hazard ratio (95% confidence interval) compared with HbA1c 5.0-5.4% of 1.46 (1.10-1.94) in men and 2.15 (1.13-4.10) in women. There was no significant association between HbA1c and hearing impairment in smokers. A J-shaped association between HbA1c and high frequency hearing impairment was observed for participants with diabetes at baseline. HbA1c was not associated

with low frequency hearing impairment among any participants.

Conclusions HbA1c ≥8.0% of non-smokers and ≥7.3% of participants with diabetes was associated with high frequency hearing impairment. These findings indicate that appropriate glycemic control may prevent diabetic-related hearing impairment.

Strengths and limitations of this study

- This study included a large number of participants, accounting for gender and smoking status.
- A median follow-up period was 5 years.
- This study findings are limited to workers in Japan.
- We investigated whether HbA1c was associated with hearing impairment among participants with diabetes at baseline.
- Information on noise exposure, ototoxic drug use, ear surgery, and ear infection was not obtained.

BACKGROUND

Patients with hearing impairment experience a range of complications, including impaired quality of life, dementia, depression, loneliness, poor self-esteem and functional disability (1-4). These complications have made this condition a social and economic problem worldwide. More than 5% of the world population has hearing impairment, and this is expected to increase with the aging of the population (5). Although this bleak picture points to the importance of identifying preventable risk factors for hearing impairment, such studies are in fact scarce.

Emerging evidence suggests that diabetes mellitus may be a risk factor for hearing impairment. Meta-analyses of 13 cross-sectional studies showed that subjects with diabetes had a 2-fold-increased risk of developing hearing impairment (odds ratio 2.15, 95%CI 1.72-2.68) (6). Diabetic hearing impairment is hypothesized to be due to microvascular complications (7, 8). Diabetic hearing impairment may thus be prevented by appropriate glycemic control, which has been shown to be effective for other microvascular complications of diabetes, such as retinopathy, nephropathy and neuropathy (9-12). Three studies have reported the association between hearing impairment and hemoglobin A1c (HbA1c), an indicator for glycemic control (13-15). One of these reported a positive dose-relationship between HbA1c and hearing

impairment as defined using a pure-tone average threshold of mainly low frequencies (15), while the other two reported that HbA1c was positively associated with high frequency hearing impairment (13, 14). Nevertheless, no study has yet reported the precise shape of the dose-relationship between HbA1c and high frequency hearing impairment. Furthermore, no study has yet investigated whether HbA1c is associated with hearing impairment among those with diabetes.

In Japan, a pure-tone audiometric test is mandatory in annual occupational health check-ups (16). The large sample size this affords has enabled us to investigate the dose-response relationship between HbA1c and hearing impairment, while accounting for well-known risk factors of hearing impairment such as gender and smoking (17, 18).

The present study had two aims. The first aim was to investigate the association between HbA1c and the incidence of hearing impairment using a large dataset from annual occupational health check-ups in Japan, accounting for gender and smoking status. The second aim was to determine whether HbA1c was associated with hearing impairment among participants with diabetes.

METHODS

Study population

The present study was conducted using data from annual health check-ups of Japanese workers. The All Japan Labor Welfare Foundation, a health service provider with centers in Tokyo, Aomori, Nagano, Yamagata, Ibaraki, Gunma and Nagoya provided the data from April 2008 through Dec 2015, allowing a maximum of 7 years of follow-up. In Japan, annual health check-ups are mandatory for all employees and include a hearing test under the Industrial Safety and Health Act. Nearly all employees attend a health check-up every year. Participants were mainly Japanese employees but also included a small number of their dependents, employers and foreign workers.

A total of 312,512 participants aged 30-65 years underwent a hearing test and HbA1c test at baseline (between Apr 2008 and Mar 2009). Of these, we excluded participants with hearing impairment at baseline (n=51,489). Given that diabetic patients with complications may receive more intensive treatments, which may bias the association between HbA1c and hearing impairment, we excluded participants with cardiovascular disease and stroke (n=913). We further excluded participants who did not attend any subsequent health examinations or hearing tests (n=48,618). After further exclusion of 8,517 participants with missing information on covariates (5,011 for smoking status, 5,152 for alcohol consumption, 1,815 for physical activity data, 5 for body mass index (BMI), 9 for hypertension and 9 for dyslipidemia data; some participants had missing

data for more than one parameter), leaving 202,975 participants (131,689 men and 71,286 women) for analysis.

Ethics

We obtained written informed consent from each participant who attended the heath check-up after April 2013. Before March 2013, we disclosed the purpose of our study by posters and the participants had the opportunity to refuse the use of their data for the study. This procedure conforms to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, where the obtaining consent may be simplified for observational studies using existing data. The research protocol including consent procedure was approved by the Ethics Committee of the Faculty of Medicine, Toho University (No. 25017 and No.A16130) and the Ethics Committee of the National Center for Global Health and Medicine (No. NCGM-G-001254-02).

Ascertainment of hearing impairment

Trained staff performed pure-tone air-conduction audiometry using an audiometer (AA-57, RION Inc., Tokyo, Japan). Low frequency hearing impairment was defined as failure to hear a pure-tone signal of 30dB at 1 kHz in the better ear, and high frequency hearing impairment as failure to hear a pure-tone signal of 40dB at 4 kHz in the better ear. These thresholds are recommended for use in annual health check-ups by Ministry

of Health, Labor and Welfare in Japan (16). Onset of hearing impairment was defined as the day of the health check-up on which hearing impairment was first detected.

Data collection and measurements at baseline (between Apr 2008 and Mar 2009)

We used a self-administered questionnaire developed by the Ministry of Health, Labor and Welfare for a specific health examination, namely the national health checkup system focused on metabolic syndrome (19), to assess medical history, regular physical activity (walking time <60 min/day or ≥60 min/day), smoking status (non-smoker, daily smoker ≤20 cigarettes/day or >20 cigarettes/day), alcohol consumption (non-drinker, <1 *go*, 1 to <2 *go* or ≥2 *go*/day; one *go* of sake, a traditional Japanese beverage, is equal to about 180 mL of 10-14% ethanol and contains about 23 g of ethanol) (20), and self-reported diabetes (treatments with anti-diabetic medication or a self-reported history of diabetes: yes or no). Job type was categorized as professional job, management, office job, sales, service, telegraph, manufacturing, transportation and other. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in metres and categorized into 4 groups (<18.5, 18.5-22.9, 23-29.9, ≥30kg/m²). Blood pressure was measured in the sitting position using an automated sphygmomanometer (HEM-907, Omron, Kyoto, Japan). Participants with high blood

pressure (≥130 mmHg systolic or ≥85 mmHg diastolic) received a second measurement and the average was used for the analysis. Hypertension was defined by ≥140 mmHg systolic, ≥90 mmHg diastolic or the use of medication for hypertension. A venous blood sample was collected and stored in a cooler at 4 °C for transportation to an external laboratory (SRL, Tokyo, Japan). Triglyceride level was measured using an enzymatic colorimetric test and high-density lipoprotein cholesterol (HDL-C) was determined using a direct method. Dyslipidemia was defined by triglyceride ≥150 mg/dL (1.7 mmol/L) in men and women, HDL-C <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or use of medication for dyslipidemia. HbA1c was measured by latex agglutination turbidimetry and converted to the National Glycohemoglobin Standardization Program equivalent value (%) using the formula below, according to the Japan Diabetes Society statement (21) :

HbA1c (%) = 1.02 ×HbA1c (Japan Diabetes Society) (%) + 0.25%

Diabetes was defined as FPG≥126mg/dL, HbA1c≥6.5%, or self-reported diabetes.

Statistical analysis

Participants were divided into 7 groups according to their HbA1c level at baseline [<5.0% (31mmol/mol), 5.0-5.4% (31-36mmol/mol), 5.5-5.9% (37-41mmol/mol), 6.0-6.4% (42-46mmol/mol), 6.5-6.9% (48-52mmol/mol), 7.0-7.9% (53-63mmol/mol),

≥8.0% (64 mmol/mol)]. The HbA1c group specific baseline characteristics of participants were described as means (SD) for continuous variables and percentages for categorical variables. Person-years was calculated from baseline to the onset of hearing impairment, or the date of the last health check-up through Dec 2015 (whichever occurred first). Crude incident rates of hearing impairment were shown in events per 1000 person-years. Survival analyses were performed using Cox regression to estimate the hazard ratio (HR) with 95% confidence interval (CI) for the incidence of hearing impairment across HbA1c categories, with 5.0-5.4% (31-36mmol/mol) as the reference value. The analyses were stratified by sex because the interaction between hearing impairments and sex was significant (p for interaction <0.001). Age-adjusted model (model 1) and multiple-adjusted model (model 2), which included alcohol consumption, physical activity, BMI, hypertension, dyslipidemia, self-reported diabetes and smoking status were used for the analysis. Although smoking status itself was related to hearing impairment in this study, the association between HbA1c and hearing impairment differed according to smoking status (p for interaction <0.001). We therefore additionally performed analyses according to combined HbA1c (7 groups) and smoking status (non-smoker and current smoker), by considering HbA1c 5.0-5.4% (31-36mmol/mol) and non-smoker as the reference category. We did not analyze

women's smokers because of the small number of cases. To assess whether control of HbA1c would reduce the incidence of hearing impairment in those with diabetes, we elucidated the shape of the relationship between HbA1c and high frequency hearing impairment among those with diabetes. We fitted restricted cubic splines models with seven knots placed at the 1th, 5th, 25th, 50th, 75th, 95th, and 99th centiles as reference values of HbA1c 6.6% (25th) (22). The HRs were adjusted for alcohol consumption, physical activity, BMI, hypertension, dyslipidemia and smoking status. As a sensitivity analysis, we further adjusted for job type in the main analyses (model 2) among participants with this information (n=126,823). We tested the proportional hazards assumption using Schoenfeld residuals. We found no significant deviations for any covariate. P value of two-tailed test <0.05 was considered statistically significant. Trend association was assessed by assigning ordinal numbers (0–6) to the HbA1c categories. We calculated the p for the quadratic trend because it was a better fit for the data than the simple linear model. All statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, Texas, USA).

Patient and public involvement

No patient were involved in setting the research question or the outcome measures, planning for the design of the study

RESULTS

Baseline characteristics by category of HbA1c are shown in Table 1. The mean age of participants was 45 years for men and 47 years for women. Participants who had higher HbA1c tended to be non-drinkers and to have higher BMI, hypertension, and dyslipidemia in both men and women. Male participants with higher HbA1c tended to be smokers consuming > 20 cigarettes per day.

In men, 4,621 developed high frequency hearing impairment with 661,937 person-years (mean duration of follow-up was 5.0 years) and 1,311 developed low frequency hearing impairment with 670,153 person-years (5.1 years). In women, 582 developed high frequency hearing impairment with 345,312 person-years (4.8 years) and 1,207 developed low frequency hearing impairment with 344,057 person-years (4.8 years). Table 2 shows the association between HbA1c and the incidence of hearing impairment. In the multivariable-adjusted model, HbA1c showed a quadratic trend with the incidence of high frequency hearing impairment in men (p for quadratic=0.007), and a statistically marginal association in women (p for quadratic=0.08). HbA1c was not associated with low frequency hearing impairment. Figure 1 shows the association between HbA1c and high frequency hearing impairment with accounting for smoking status [the interaction between HbA1c and smoking status (p for interaction <0.001)].

Compared to non-smokers with HbA1c 5.0-5.4% (31-36mmol/mol), non-smokers with HbA1c ≥8.0% (64 mmol/mol) showed an association with hearing impairment [HR (95%CI) of 1.46 (1.11-1.92) in men and 2.36 (1.34-4.15) in women]. Although smokers had higher HRs of hearing impairment than non-smokers, HbA1c level was not associated with hearing impairment among smokers. Additional adjustments for job type did not affect the results (Appendix 1).

Figure 2 shows the spline regression model of high frequency hearing impairment at various HbA1c levels against a reference HbA1c level of 6.6% in participants with diabetes at baseline (n=10,154). The relationship between HbA1c and the incidence of hearing impairment was J-shaped, with the significant increase of HR for HbA1c≥7.2%.

DISCUSSION

In this study, we found a quadratic trend between HbA1c and the incidence of high frequency hearing impairment. In particular, HbA1c concentrations over 8.0% (64 mmol/mol) were associated with high frequency hearing impairment among non-smokers. A J-shaped association between HbA1c and high frequency hearing impairment was observed among participants with diabetes at baseline. Our findings

indicate that appropriate glycemic control may prevent the incidence of diabetic hearing impairment.

Our finding of a quadratic trend between HbA1c and hearing impairment is supported by the results of two longitudinal studies. (13, 15) One of these reported an odds ratio (95% CI) of high frequency hearing impairment per 1.0% increase in HbA1c of 1.52 (1.03 to 2.23), albeit no statistical association between the three categories of HbA1c and high frequency hearing impairment (13). The second reported that HbA1c was positively associated with average hearing threshold, mainly among low frequencies (15). The present study provides novel evidence that an HbA1c of 8.0% (64 mmol/mol) or above is associated with increased risk of high frequency hearing impairment in non-smokers. Our findings are consistent with the work of Cruickshanks et al., who reported that poor glycemic control, defined by a glycosylated hemoglobin level, was associated with hearing impairment (23).

Additionally, we found that the J-shaped association between HbA1c and hearing impairment remained even among participants with diabetes at baseline. This result suggests that proper glycemic control may prevent diabetic-related hearing impairment even in those with diabetes. Previous studies have also reported a J-shaped association between HbA1c and diabetics complications, and noted that hypoglycemia

might increase diabetic complications (24-26). More research is needed to determine a suitable HbA1c level for glycemic targeting to prevent hearing impairment in diabetic management.

We found that high frequency hearing impairment has a quadratic trend with HbA1c among non-smokers but not smokers. Previous studies have reported an adverse effect of smoking cigarettes on hearing impairment (23, 27, 28). It is plausible that the effect of smoking cigarettes may be stronger than HbA1c and might mask the effect of HbA1c. Further research is needed to confirm the joint effect of smoking and HbA1c on hearing impairment.

The pathophysiology underlying high-HbA1c-associated hearing impairment is unclear, which allows for speculation. One possible explanation is that hyperglycemia-related microvascular complications lead to thickening of the cochlea and vestibulopathy, and result in hearing impairment (7, 8, 29-33). Diabetic-related hearing impairment has been mainly observed at high frequencies, suggesting that high frequency-specific areas of the cochlea may be more fragile to ischemic changes due to microvascular complications (34-38). This mechanism is supported by the J-shaped association between HbA1c and hearing impairment observed in the present study, since

previous studies also reported a J-shaped-association between HbA1c and diabetic vascular complications (39, 40). Further studies to confirm this idea are required.

This study has several strengths. The large dataset allowed us to investigate the association between HbA1c and hearing impairment with comprehensive adjustment for covariates, and additionally, among participants with diabetes at baseline. Audiometry to confirm hearing impairment was conducted by trained staff. Several limitations of the study also need to be considered. First, though noise exposure is an important risk factor on hearing impairment (41, 42), information on noise exposure was not available and thus noise information was not considered in the analyses. The present study thus might include the cofounding influence of noise exposure. However, a previous study reported that the relationship between diabetes and hearing impairment was independent of this variable (37). Moreover, in the present study, HbA1c level was associated with hearing impairment even after accounting for job type in a sensitivity analysis. Second, information on ototoxic drug use, ear surgery, and ear infection was not collected, and we were therefore unable to exclude cases of hearing impairment due to these factors. Third, blood pressure was measured once, followed by a second measurement if the first systolic blood pressure ≥130 mmHg systolic or diastolic blood pressure ≥85 mmHg. All participants didn't have the same evaluation of blood pressure. This may lead to

misclassification of hypertension. Fourth, we did not account for gender or smoking status in the association between HbA1c and hearing impairment for participants with diabetes because of the small sample size. Fifth, the hearing test was only conducted at 1 kHz and 4 kHz. Hearing impairment at other frequencies could not therefore be identified. Sixth, we cannot exclude the possibility of residual confounding and confounding by unmeasured variables. Finally, the study participants were mainly workers, and thus caution is required when generalizing our findings.

CONCLUSION

We found the quadratic trend between HbA1c and the incidence of high frequency hearing impairment in non-smokers. The trend between HbA1c and hearing impairment remained even among those with diabetes. These findings indicate that diabetic-related hearing impairment may be prevented with appropriate glycemic control. These findings warrant confirmation in interventional studies.

Abbreviations

HbA1c: hemoglobin A1c; BMI: body mass index; HR: hazard ratio; CI: confidence interval

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Contributors

SN, TaM and IK designed study and drafted the manuscript. SN, HHH, KaK, AN and KeK performed the data analysis. MD collected and interpreted the data. All authors participated in interpretation of the findings, revised the paper critically for important intellectual content and approved the final version to be published. YN and YM provided administrative, technical and material support. TM and SA revised the work critically for important intellectual content. SN and YN are guarantors.

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Competing interests

SN is occupational physicians in All Japan Labor Welfare Foundation. All Japan Labor Welfare Foundation had no role in the design, analysis or writing of this articles. All other authors declare no competing financial interests.

Ethics approval

The research protocol was approved by the Ethics Committee of the Faculty of Medicine, Toho University and the Ethics Committee of the National Center for Global Health and Medicine.

Data sharing statement

No additional data are available.

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Table 1 Baseline characteristics of study participants according to HbA_{1c} (n=202,975).

		HbA_{1c} (%) (mmol/mol)						
	Overall	<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)
Men								
n	131,689	10,701	53,839	50,957	8,995	2,488	2,224	2,485
Age (years)*	44.6 (9.1)	40.9 (8.2)	42.6 (8.6)	45.7 (9.0)	49.6 (8.6)	51.7 (7.9)	51.6 (7.8)	49.2 (8.2)
Walking time, ≥60 min/day (%)	16	16	17	17	15	15	16	13
Smoking status (%)								
Non-smoker	45.15	44	44	46	47	50	46	40
Daily consuming ≤20 cigarettes/day	37.04	39	39	36	34	31	32	35
Daily consuming >20 cigarettes/day	17.8	17	17	18	19	19	22	25
Alcohol consumption (%)								
Non-drinker	26	19	24	29	31	30	33	36
Drinker <1 *go*/day†	35	32	35	36	34	34	30	32
Drinker 1 to <2 *go*/day†	26	30	27	25	25	25	26	22
Drinker ≥2 *go*/day†	12	19	13	10	10	11	11	10
Self-reported diabetes (%)‡	2.3	0.07	0.10	0.4	4.6	22.4	41.1	37.3
BMI (kg/m2)*	23.8 (3.5)	22.6 (2.9)	23.2 (3.1)	24.0 (3.5)	25.4 (4.0)	26.0 (4.2)	26.3 (4.3)	26.4 (4.5)
Hypertension (%)§	28	21	22	29	44	57	57	53
Dyslipidemia (%)ǀ	39	29	33	41	54	59	60	65
Women								
n	71,286	5,880	28,277	29,741	5,286	890	618	594
Age (years)*	47.1 (9.0)	41.5 (7.6)	44.6 (8.6)	49.0 (8.6)	52.6 (7.6)	53.9 (7.2)	53.9 (7.2)	52.0 (7.6)
Walking time, ≥60 min/day (%)	12	11	11	12	13	12	13	11
Smoking status (%)								
Non-smoker	80	71	77	83	86	86	83	77
Daily consuming ≤20 cigarettes/day	19	26	21	16	13	13	16	22
Daily consuming >20 cigarettes/day	1.4	2.5	1.5	1.2	1.2	1.1	1.5	1.9
Alcohol consumption (%)								
Non-drinker	60	45	56	65	70	74	73	78
Drinker <1 *go*/day†	31	36	34	29	26	22	22	19
Drinker 1 to <2 *go*/day†	6.8	14.4	7.8	5.0	3.8	3.9	3.7	2.7
Drinker ≥2 *go*/day†	1.7	5.3	1.9	1.0	0.5	0.6	0.5	0.7
Self-reported diabetes (%)‡	1.2	0.05	0.03	0.1	2.5	17.4	38.2	47.5
BMI (kg/m2)*	22.3 (3.6)	21.2 (2.9)	21.6 (3.2)	22.5 (3.7)	23.9 (4.3)	25.5 (4.7)	26.4 (4.8)	26.6 (4.6)
Hypertension (%)§	19	11	14	21	34	52	59	53
Dyslipidemia (%)ǀ	22	13	16	24	39	54	61	59

Longitudinal survey of 202,950 examinees in All Japan Labor Welfare Foundation, Japan, 2008.

* Mean (SD)

† One *go* contains ~23g of ethanol.

‡ Self-reported diagnosis of diabetes or receiving medication.

§ Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication.

ǀ Triglyceride level ≥150mg/dL (1.7mmol/L), high-density lipoprotein cholesterol level <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.3 mml/L) in women or receiving medication.

Table 2 Hazard ratio of hearing impairment according to baseline HbA_{1c} (n = 202,975).

		HbA_{1c} (%) (mmol/mol)							
		<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)	P for quadratic
Low frequency									
Men	Person-year	54,055	275,953	261,290	44,807	11,798	10,637	11,613	
	No. cases	84	447	548	122	45	26	39	
	Model 1	1.15 (0.91 to 1.45)	1.00	0.98 (0.86 to 1.11)	0.94 (0.77 to 1.15)	1.11 (0.81 to 1.51)	0.73 (0.49 to 1.08)	1.22 (0.88 to 1.70)	0.15
	Model 2	1.11 (0.88 to 1.40)	1.00	1.00 (0.88 to 1.14)	0.98 (0.79 to 1.20)	1.16 (0.84 to 1.60)	0.75 (0.49 to 1.15)	1.26 (0.88 to 1.80)	0.27
Women	Person-year	28,447	137,761	143,295	25,083	4,136	2,760	2,576	
	No. cases	65	415	553	133	18	14	9	
	Model 1	1.04 (0.80 to 1.35)	1.00	0.90 (0.79 to 1.03)	0.94 (0.77 to 1.14)	0.71 (0.44 to 1.14)	0.86 (0.51 to 1.48)	0.68 (0.35 to 1.31)	0.79
	Model 2	1.04 (0.80 to 1.35)	1.00	0.91 (0.80 to 1.03)	0.93 (0.76 to 1.14)	0.67 (0.41 to 1.10)	0.77 (0.43 to 1.38)	0.57 (0.28 to 1.19)	0.51
High frequency									
Men	Person-year	53,617	273,025	257,812	44,093	11,621	10,345	11,424	
	No. cases	280	1,610	1,941	416	116	128	130	
	Model 1	1.05 (0.92 to 1.19)	1.00	0.98 (0.91 to 1.04)	0.91 (0.82 to 1.02)	0.82 (0.67 to 0.99)	1.05 (0.88 to 1.26)	1.15 (0.96 to 1.38)	0.003
	Model 2	1.03 (0.90 to 1.17)	1.00	0.99 (0.92 to 1.06)	0.93 (0.83 to 1.03)	0.84 (0.69 to 1.02)	1.08 (0.89 to 1.32)	1.18 (0.97 to 1.43)	0.007
Women	Person-year	28,520	138,232	143,882	25,246	4,124	2,753	2,555	
	No. cases	23	169	277	67	18	13	15	
	Model 1	1.02 (0.66 to 1.58)	1.00	1.00 (0.83 to 1.22)	0.97 (0.73 to 1.29)	1.43 (0.88 to 2.34)	1.62 (0.92 to 2.86)	2.41 (1.42 to 4.10)	0.03
	Model 2	1.03 (0.66 to 1.60)	1.00	0.97 (0.80 to 1.17)	0.86 (0.64 to 1.16)	1.17 (0.70 to 1.95)	1.24 (0.67 to 2.29)	1.78 (0.95 to 3.34)	0.08

Model 1: Adjusted for age.

Model 2: Adjusted for age, walking time, smoking status, alcohol consumption, self-reported diabetes, BMI, hypertension and hyperlipidemia.

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Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.
Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), self-reported diabetes, hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving medication).

Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5, p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), smoking status (non-smoker, smoker consuming ≤ 20, or > 20 cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

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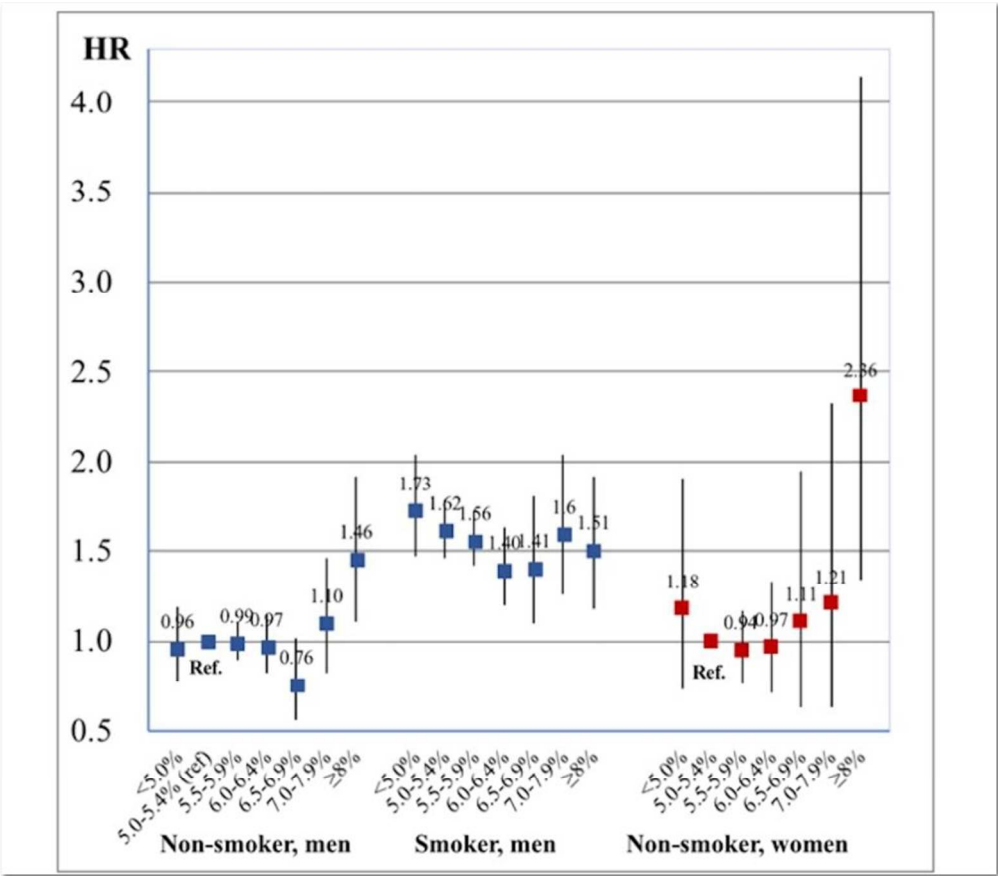

Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.

Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), self-reported diabetes, hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving medication).

84x73mm (300 x 300 DPI)

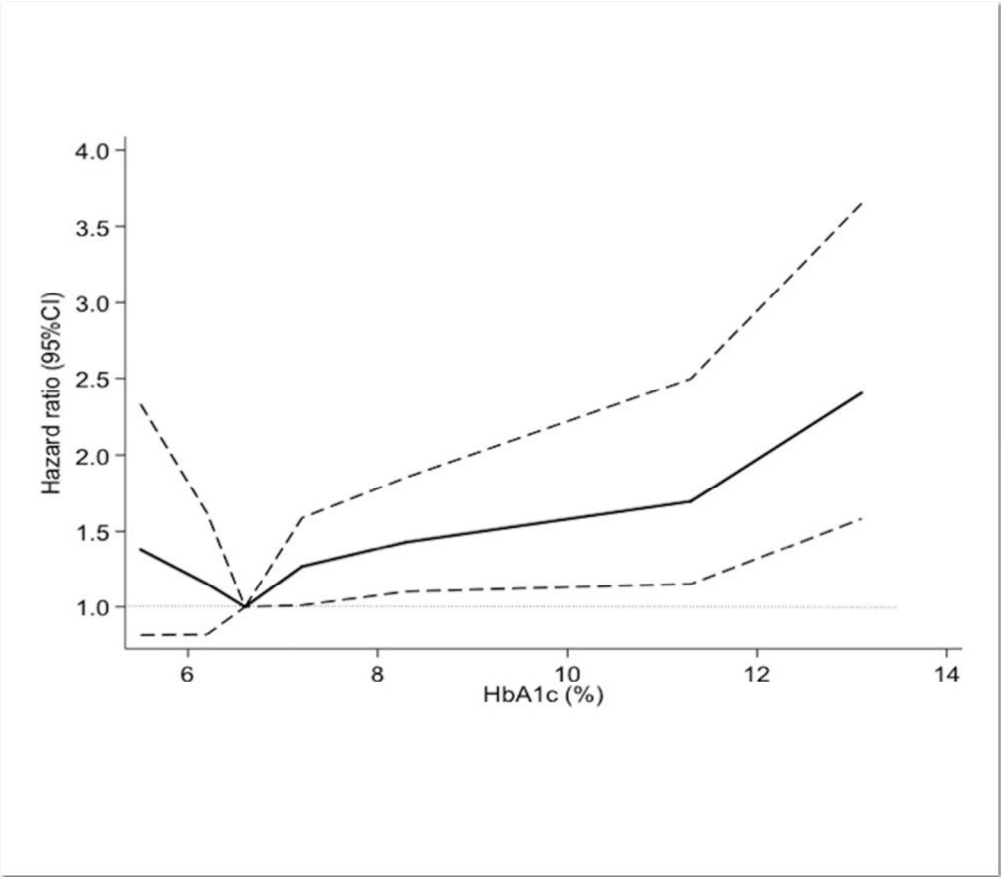

Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5, p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or ≥ 30.0 kg/m2), smoking status (non-smoker, smoker consuming ≤ 20, or > 20 cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or ≥ 2 go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or ≥60 min/day), hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication), and hyperlipidemia (triglyceride level ≥150mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

84x73mm (300 x 300 DPI)

Appendix 1. The association between baseline HbA_{1c} and Incidence of high frequency hearing impairment (n=126,823).

		HbA_{1c} (%) (mmol/mol)							
		<5.0 (<31)	5.0-5.4 (31-36)	5.5-5.9 (37-41)	6.0-.6.4 (42-46)	6.5-6.9 (48-52)	7.0-7.9 (53-63)	≥8 (≥64)	P for quadratic
Men	Person-year	44,265	227,740	215,647	36,368	9,184	8,148	8,888	
	No.cases	229	1,345	1,535	329	91	99	100	
	non-smoker	0.94 (0.73 to 1.20)	1.00	0.93 (0.82 to 1.05)	0.89 (0.73 to 1.07)	0.68 (0.48 to 0.96)	1.10 (0.80 to 1.53)	1.37 (1.00 to 1.88)	0.01
	smoker	1.06 (0.89 to 1.26)	1.00	0.95 (0.86 to 1.05)	0.91 (0.77 to 1.07)	1.00 (0.76 to 1.31)	1.10 (0.84 to 1.44)	1.04 (0.79 to 1.37)	0.23
Women	Person-year	22,749	110,979	114,327	19,601	3,143	2,062	1,813	
	No.cases	19	140	214	48	15	11	13	
	non-smoker	1.11 (0.65 to 1.91)	1.00	0.92 (0.72 to 1.18)	0.88 (0.61 to 1.26)	1.28 (0.69 to 2.35)	1.47 (0.73 to 2.94)	2.83 (1.53 to 5.24)	0.005

Adjusted for age, walking time, alcohol consumption, self-reported diabetes, BMI, hypertension, hyperlipidemia and job type.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1 Line1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P3 Line31, P4 Line51
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P5 Line64-79
Objectives	3	State specific objectives, including any prespecified hypotheses	P6 Line83-88
Methods			
Study design	4	Present key elements of study design early in the paper	P7 Line90
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P7 Line90-107
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P7 Line99-108
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P8 Line118-155
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	P9 Line143-153
Bias	9	Describe any efforts to address potential sources of bias	P15 Line271-278, Line282
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P9 Line127-143
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P10 Line157-193
		(*b*) Describe any methods used to examine subgroups and interactions	P11 Line173-

	184
(*c*) Explain how missing data were addressed	P7 Line105-107
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	P12 Line185-187

Continued on next page

Results			
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	Table1,2, Fig2
		(b) Give reasons for non-participation at each stage	P11 Line178
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P12 Line196-200, Table1
		(b) Indicate number of participants with missing data for each variable of interest	P7 Line1001-109
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	P12 Line201-206
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	P12 Line200-206
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
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	P13 Line215
		(*b*) Report category boundaries when continuous variables were categorized	P10 Line158-161
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P14 Line218-223
Discussion			
Key results	18	Summarise key results with reference to study objectives	P14 Line225-231
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	P17 Line271-284
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P17 Line285-290
Generalisability	21	Discuss the generalisability (external validity) of the study results	P17 Line284-

			285
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	P18 Line301

*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.