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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023220
Article Type:	Research
Date Submitted by the Author:	29-Mar-2018
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Keywords:	EPIDEMIOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, OCCUPATIONAL & INDUSTRIAL MEDICINE, Audiology < OTOLARYNGOLOGY

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Manuscripts

1 **Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large**

2 **occupational health check-up data of Japan**

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39 31 Word count 3,091

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42 32 Tables 2

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6 34 **Objectives** The aim of this study was to determine whether hemoglobin A1c (HbA1c)  
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9 35 level is associated with the incidence of hearing impairment accounting for smoking  
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12 36 status and diabetic condition at baseline.

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14 37 **Methods** Participants were 131,689 men and 71,286 women aged 30-65 years and free  
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17 38 of hearing impairment at baseline (2008) who attended annual health check-ups from  
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20 39 2008 to 2015. We defined low frequency hearing impairment at a hearing threshold >30  
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23 40 dB at 1 kHz and high frequency at >40 dB at 4 kHz in the better ear in pure-tone  
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26 41 audiometric tests. HbA1c was categorized into 7 categories. The association between  
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28  
29 42 HbA1c and hearing impairment was assessed using the Cox proportional hazards  
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32 43 model.

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34 44 **Results** On 5 years' mean follow-up, high HbA1c was associated with high frequency  
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37 45 hearing impairment. In non-smokers, HbA1c  $\geq 8.0\%$  was associated with high frequency  
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39  
40 46 hearing impairment, with a multivariable hazard ratio (95% confidence interval)  
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42  
43 47 compared with HbA1c 5.0-5.4% of 1.46 (1.10-1.94) in men and 2.15 (1.13-4.10) in  
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45  
46 48 women. There was no significant association between HbA1c and hearing impairment  
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48  
49 49 in smokers. A J-shaped association between HbA1c and high frequency hearing  
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52 50 impairment was observed for participants with diabetes at baseline. HbA1c was not  
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55 51 associated with low frequency hearing impairment among any participants.  
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6 52 **Conclusions** HbA1c  $\geq$ 8.0% of non-smokers and  $\geq$ 7.3% of participants with diabetes  
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9 53 was associated with high frequency hearing impairment. These findings indicate that  
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11 54 appropriate glycemic control may prevent diabetic-related hearing impairment.  
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17 56 Strengths and limitations of this study

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20 57 ▪ This study included a large number of participants, accounting for gender and smoking  
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22 58 status.

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25 59 ▪ To determine whether HbA1c was associated with hearing impairment among  
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27 60 participants with diabetes at baseline.

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30 61 ▪ Information on ototoxic drug use, ear surgery, and ear infection was was not obtained.  
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6 64 BACKGROUND

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8 65 Patients with hearing impairment experience a range of complications, including  
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11 66 impaired quality of life, dementia, depression, loneliness, poor self-esteem and  
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14 67 functional disability (1-4). These complications have made this condition a social and  
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17 68 economic problem worldwide. More than 5% of the world population has hearing  
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20 69 impairment, and this is expected to increase with the aging of the population (5).  
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23 70 Although this bleak picture points to the importance of identifying preventable risk  
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26 71 factors for hearing impairment, such studies are in fact scarce.  
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29 72 Emerging evidence suggests that diabetes mellitus may be a risk factor for hearing  
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32 73 impairment. Meta-analyses of 13 cross-sectional studies showed that subjects with  
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35 74 diabetes had a 2-fold-increased risk of developing hearing impairment (odds ratio 2.15,  
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38 75 95%CI 1.72-2.68) (6). Diabetic hearing impairment is hypothesized to be due to  
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41 76 microvascular complications (7, 8). Diabetic hearing impairment may thus be prevented  
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44 77 by appropriate glycemetic control, which has been shown to be effective for other  
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47 78 microvascular complications of diabetes, such as retinopathy, nephropathy and  
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50 79 neuropathy (9-12). Three studies have reported the association between hearing  
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53 80 impairment and hemoglobin A1c (HbA1c), an indicator for glycemetic control (13-15).  
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56 81 One of these reported a positive dose-relationship between HbA1c and hearing  
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6 82 impairment as defined using a pure-tone average threshold of mainly low frequencies  
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9 83 (15), while the other two reported that HbA1c was positively associated with high  
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11 84 frequency hearing impairment (13, 14). Nevertheless, no study has yet reported the  
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14 85 precise shape of the dose-relationship between HbA1c and high frequency hearing  
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17 86 impairment. Furthermore, no study has yet investigated whether HbA1c is associated  
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20 87 with hearing impairment among those with diabetes.  
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23 88 In Japan, a pure-tone audiometric test is mandatory in annual occupational health  
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26 89 check-ups (16). The large sample size this affords has enabled us to investigate the  
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29 90 dose-response relationship between HbA1c and hearing impairment, while accounting  
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32 91 for well-known risk factors of hearing impairment such as gender and smoking (17, 18).  
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34  
35 92 The present study had two aims. The first aim was to investigate the association  
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38 93 between HbA1c and the incidence of hearing impairment using a large dataset from  
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41 94 annual occupational health check-ups in Japan, accounting for gender and smoking  
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44 95 status. The second aim was to determine whether HbA1c was associated with hearing  
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47 96 impairment among participants with diabetes.

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## 49 98 METHODS

### 50 99 Study population



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6 100 The present study was conducted using data from annual health check-ups of Japanese  
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9 101 workers. The All Japan Labor Welfare Foundation, a health service provider with  
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11 102 centers in Tokyo, Aomori, Nagano, Yamagata, Ibaraki, Gunma and Nagoya provided the  
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14 103 data from April 2008 through Dec 2015, allowing a maximum of 7 years of follow-up.  
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17 104 In Japan, annual health check-ups are mandatory for all employees and include a  
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20 105 hearing test under the Industrial Safety and Health Act. Nearly all employees attend a  
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23 106 health check-up every year. Participants were mainly Japanese employees but also  
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26 107 included a small number of their dependents, employers and foreign workers.  
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29 108 A total of 312,512 participants aged 30-65 years underwent a hearing test and HbA1c  
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31 109 test at baseline (between Apr 2008 and Mar 2009). Of these, we excluded participants  
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34 110 with hearing impairment at baseline (n=51,489). Given that diabetic patients with  
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37 111 complications may receive more intensive treatments, which may bias the association  
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40 112 between HbA1c and hearing impairment, we excluded participants with cardiovascular  
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43 113 disease and stroke (n=913). We further excluded participants who did not attend any  
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46 114 subsequent health examinations or hearing tests (n=48,618). After further exclusion of  
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49 115 8,517 participants with missing information on covariates (5,011 for smoking status,  
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51 116 5,152 for alcohol consumption, 1,815 for physical activity data, 5 for body mass index  
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54 117 (BMI), 9 for hypertension and 9 for dyslipidemia data; some participants had missing  
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6 118 data for more than one parameter), leaving 202,975 participants (131,689 men and

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9 119 71,286 women) for analysis.

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12 120 Ethics

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14 121 We obtained written informed consent from each participant who attended the health

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17 122 check-up after April 2013. Before March 2013, we disclosed the purpose of our study

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20 123 by posters and the participants had the opportunity to refuse the use of their data for the

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23 124 study. This procedure conforms to the Japanese Ethical Guidelines for Medical and

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26 125 Health Research Involving Human Subjects, where the obtaining consent may be

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29 126 simplified for observational studies using existing data. The research protocol including

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32 127 consent procedure was approved by the Ethics Committee of the Faculty of Medicine,

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35 128 Toho University (No. 25017 and No.A16130) and the Ethics Committee of the National

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38 129 Center for Global Health and Medicine (No. NCGM-G-001254-02).

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40 130 Ascertainment of hearing impairment

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43 131 Trained staff performed pure-tone air-conduction audiometry using an audiometer

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46 132 (AA-57, RION Inc., Tokyo, Japan). Low frequency hearing impairment was defined as

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49 133 failure to hear a pure-tone signal of 30dB at 1 kHz in the better ear, and high frequency

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52 134 hearing impairment as failure to hear a pure-tone signal of 40dB at 4 kHz in the better

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55 135 ear. These thresholds are recommended for use in annual health check-ups by Ministry

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6 136 of Health, Labor and Welfare in Japan (16). Onset of hearing impairment was defined as  
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9 137 the day of the health check-up on which hearing impairment was first detected.  
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11 138 Data collection and measurements at baseline (between Apr 2008 and Mar 2009)  
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14 139 We used a self-administered questionnaire developed by the Ministry of Health, Labor  
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17 140 and Welfare for a specific health examination, namely the national health checkup  
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20 141 system focused on metabolic syndrome (19), to assess medical history, regular physical  
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23 142 activity (walking time  $<60$  min/day or  $\geq 60$  min/day), smoking status (non-smoker, daily  
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26 143 smoker  $\leq 20$  cigarettes/day or  $>20$  cigarettes/day), alcohol consumption (non-drinker,  $<1$   
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29 144 *go*, 1 to  $<2$  *go* or  $\geq 2$  *go*/day; one *go* of sake, a traditional Japanese beverage, is equal to  
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32 145 about 180 mL of 10-14% ethanol and contains about 23 g of ethanol) (20), and  
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35 146 self-reported diabetes (treatments with anti-diabetic medication or a self-reported  
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38 147 history of diabetes: yes or no). Job type was categorized as professional job,  
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41 148 management, office job, sales, service, telegraph, manufacturing, transportation and  
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44 149 other. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body  
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47 150 mass index (BMI) was calculated as the weight in kilograms divided by the square of  
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50 151 height in metres and categorized into 4 groups ( $<18.5$ , 18.5-22.9, 23-29.9,  $\geq 30$  kg/m<sup>2</sup>).  
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53 152 Blood pressure was measured in the sitting position using an automated  
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56 153 sphygmomanometer (HEM-907, Omron, Kyoto, Japan). Participants with high blood

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6 154 pressure ( $\geq 130$  mmHg systolic or  $\geq 85$  mmHg diastolic) received a second measurement  
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9 155 and the average was used for the analysis. Hypertension was defined by  $\geq 140$  mmHg  
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11 156 systolic,  $\geq 90$  mmHg diastolic or the use of medication for hypertension. A venous blood  
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14 157 sample was collected and stored in a cooler at 4 °C for transportation to an external  
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17 158 laboratory (SRL, Tokyo, Japan). Triglyceride level was measured using an enzymatic  
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20 159 colorimetric test and high-density lipoprotein cholesterol (HDL-C) was determined  
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23 160 using a direct method. Dyslipidemia was defined by triglyceride  $\geq 150$  mg/dL (1.7  
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26 161 mmol/L) in men and women, HDL-C  $< 40$  mg/dL (1.04 mmol/L) in men and  $< 50$  mg/dL  
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28  
29 162 (1.3 mmol/L) in women or use of medication for dyslipidemia. HbA1c was measured by  
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32 163 latex agglutination turbidimetry and converted to the National Glycohemoglobin  
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35 164 Standardization Program equivalent value (%) using the formula below, according to the  
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38 165 Japan Diabetes Society statement (21) :  
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40 166  $\text{HbA1c (\%)} = 1.02 \times \text{HbA1c (Japan Diabetes Society) (\%)} + 0.25\%$   
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43 167 Diabetes was defined as  $\text{FPG} \geq 126$  mg/dL,  $\text{HbA1c} \geq 6.5\%$ , or self-reported diabetes.  
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46 168 Statistical analysis  
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49 169 Participants were divided into 7 groups according to their HbA1c level at baseline  
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52 170 [ $< 5.0\%$  (31 mmol/mol), 5.0-5.4% (31-36 mmol/mol), 5.5-5.9% (37-41 mmol/mol),  
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55 171 6.0-6.4% (42-46 mmol/mol), 6.5-6.9% (48-52 mmol/mol), 7.0-7.9% (53-63 mmol/mol),  
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6 172  $\geq 8.0\%$  (64 mmol/mol)]. The HbA1c group specific baseline characteristics of  
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9 173 participants were described as means (SD) for continuous variables and percentages for  
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11 174 categorical variables. Person-years was calculated from baseline to the onset of hearing  
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14 175 impairment, or the date of the last health check-up through Dec 2015 (whichever  
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17 176 occurred first). Crude incident rates of hearing impairment were shown in events per  
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20 177 1000 person-years. Survival analyses were performed using Cox regression to estimate  
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23 178 the hazard ratio (HR) with 95% confidence interval (CI) for the incidence of hearing  
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26 179 impairment across HbA1c categories, with 5.0-5.4% (31-36mmol/mol) as the reference  
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29 180 value. The analyses were stratified by sex because the interaction between hearing  
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31 181 impairments and sex was significant ( $p$  for interaction  $<0.001$ ). Age-adjusted model  
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34 182 (model 1) and multiple-adjusted model (model 2), which included alcohol consumption,  
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37 183 physical activity, BMI, hypertension, dyslipidemia, self-reported diabetes and smoking  
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40 184 status were used for the analysis. Although smoking status itself was related to hearing  
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43 185 impairment in this study, the association between HbA1c and hearing impairment  
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46 186 differed according to smoking status ( $p$  for interaction  $<0.001$ ). We therefore  
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49 187 additionally performed analyses according to combined HbA1c (7 groups) and smoking  
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52 188 status (non-smoker and current smoker), by considering HbA1c 5.0-5.4%  
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54 189 (31-36mmol/mol) and non-smoker as the reference category. We did not analyze  
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6 190 women's smokers because of the small number of cases. To assess whether control of  
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9 191 HbA1c would reduce the incidence of hearing impairment in those with diabetes, we  
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11 192 elucidated the shape of the relationship between HbA1c and high frequency hearing  
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14 193 impairment among those with diabetes. We fitted restricted cubic splines models with  
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17 194 seven knots placed at the 1th, 5th, 25th, 50th, 75th, 95th, and 99th centiles as reference  
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20 195 values of HbA1c 6.6% (25th) (22). The HRs were adjusted for alcohol consumption,  
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23 196 physical activity, BMI, hypertension, dyslipidemia and smoking status. As a sensitivity  
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26 197 analysis, we further adjusted for job type in the main analyses (model 2) among  
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29 198 participants with this information (n=126,823). We tested the proportional hazards  
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32 199 assumption using Schoenfeld residuals. We found no significant deviations for any  
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35 200 covariate. P value of two-tailed test <0.05 was considered statistically significant. Trend  
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38 201 association was assessed by assigning ordinal numbers (0–6) to the HbA1c categories.  
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41 202 We calculated the p for the quadratic trend because it was a better fit for the data than  
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44 203 the simple linear model. All statistical analyses were performed using Stata version 12.1  
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47 204 (StataCorp, College Station, Texas, USA).

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51 206 RESULTS

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6 207 Baseline characteristics by category of HbA1c are shown in Table 1. The mean age of  
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9 208 participants was 45 years for men and 47 years for women. Participants who had higher  
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11 209 HbA1c tended to be non-drinkers and to have higher BMI, hypertension, and  
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14 210 dyslipidemia in both men and women. Male participants with higher HbA1c tended to  
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17 211 be smokers consuming > 20 cigarettes per day.  
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20 212 In men, 4,621 developed high frequency hearing impairment with 661,937 person-years  
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23 213 (mean duration of follow-up was 5.0 years) and 1,311 developed low frequency hearing  
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25  
26 214 impairment with 670,153 person-years (5.1 years). In women, 582 developed high  
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29 215 frequency hearing impairment with 345,312 person-years (4.8 years) and 1,207  
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32 216 developed low frequency hearing impairment with 344,057 person-years (4.8 years).  
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34 217 Table 2 shows the association between HbA1c and the incidence of hearing impairment.  
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37 218 In the multivariable-adjusted model, HbA1c showed a quadratic trend with the  
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40 219 incidence of high frequency hearing impairment in men (p for quadratic=0.007), and a  
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43 220 statistically marginal association in women (p for quadratic=0.08). HbA1c was not  
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46 221 associated with low frequency hearing impairment. Figure 1 shows the association  
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49 222 between HbA1c and high frequency hearing impairment with accounting for smoking  
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52 223 status [the interaction between HbA1c and smoking status (p for interaction <0.001)].  
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54 224 Compared to non-smokers with HbA1c 5.0-5.4% (31-36mmol/mol), non-smokers with  
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6 225 HbA1c  $\geq$ 8.0% (64 mmol/mol) showed an association with hearing impairment [HR  
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8 226 (95%CI) of 1.46 (1.11-1.92) in men and 2.36 (1.34-4.15) in women]. Although smokers  
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11 227 had higher HRs of hearing impairment than non-smokers, HbA1c level was not  
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14 228 associated with hearing impairment among smokers. Additional adjustments for job  
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17 229 type did not affect the results (Appendix 1).

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20 230 Figure 2 shows the spline regression model of high frequency hearing impairment at  
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23 231 various HbA1c levels against a reference HbA1c level of 6.6% in participants with  
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26 232 diabetes at baseline (n=10,154). The relationship between HbA1c and the incidence of  
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29 233 hearing impairment was J-shaped, with the significant increase of HR for HbA1c $\geq$ 7.2%.

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## 32 33 34 235 DISCUSSION

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37 236 In this study, we found a quadratic trend between HbA1c and the incidence of high  
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40 237 frequency hearing impairment. In particular, HbA1c concentrations over 8.0% (64  
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43 238 mmol/mol) were associated with high frequency hearing impairment among  
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46 239 non-smokers. A J-shaped association between HbA1c and high frequency hearing  
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49 240 impairment was observed among participants with diabetes at baseline. Our findings  
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52 241 indicate that appropriate glycemic control may prevent the incidence of diabetic hearing  
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54  
55 242 impairment.



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6 243 Our finding of a quadratic trend between HbA1c and hearing impairment is supported  
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9 244 by the results of two longitudinal studies. (13, 15) One of these reported an odds ratio  
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11 245 (95% CI) of high frequency hearing impairment per 1.0% increase in HbA1c of 1.52  
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14 246 (1.03 to 2.23), albeit no statistical association between the three categories of HbA1c  
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17 247 and high frequency hearing impairment (13). The second reported that HbA1c was  
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20 248 positively associated with average hearing threshold, mainly among low frequencies  
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23 249 (15). The present study provides novel evidence that an HbA1c of 8.0% (64 mmol/mol)  
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26 250 or above is associated with increased risk of high frequency hearing impairment in  
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29 251 non-smokers. Our findings are consistent with the work of Cruickshanks et al., who  
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31  
32 252 reported that poor glycemic control, defined by a glycosylated hemoglobin level, was  
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35 253 associated with hearing impairment (23).  
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37 254 Additionally, we found that the J-shaped association between HbA1c and hearing  
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40 255 impairment remained even among participants with diabetes at baseline. This result  
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42  
43 256 suggests that proper glycemic control may prevent diabetic-related hearing impairment  
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45  
46 257 even in those with diabetes. Previous studies have also reported a J-shaped association  
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49 258 between HbA1c and diabetics complications, and noted that hypoglycemia might  
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52 259 increase diabetic complications (24-26). More research is needed to determine a suitable  
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6 260 HbA1c level for glycemic targeting to prevent hearing impairment in diabetic  
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9 261 management.  
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11 262 We found that high frequency hearing impairment has a quadratic trend with HbA1c  
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14 263 among non-smokers but not smokers. Previous studies have reported an adverse effect  
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17 264 of smoking cigarettes on hearing impairment (23, 27, 28). It is plausible that the effect  
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20 265 of smoking cigarettes may be stronger than HbA1c and might mask the effect of HbA1c.  
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22  
23 266 Further research is needed to confirm the joint effect of smoking and HbA1c on hearing  
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26 267 impairment.  
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28 268 The pathophysiology underlying high-HbA1c-associated hearing impairment is unclear,  
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30  
31 269 which allows for speculation. One possible explanation is that hyperglycemia-related  
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34 270 microvascular complications lead to thickening of the cochlea and vestibulopathy, and  
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37 271 result in hearing impairment (7, 8, 29-33). Diabetic-related hearing impairment has been  
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40 272 mainly observed at high frequencies, suggesting that high frequency-specific areas of  
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43 273 the cochlea may be more fragile to ischemic changes due to microvascular  
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46 274 complications (34-38). This mechanism is supported by the J-shaped association  
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49 275 between HbA1c and hearing impairment observed in the present study, since previous  
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52 276 studies also reported a J-shaped-association between HbA1c and diabetic vascular  
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55 277 complications (39, 40). Further studies to confirm this idea are required.  
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6 278 This study has several strengths. The large dataset allowed us to investigate the  
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8 279 association between HbA1c and hearing impairment with comprehensive adjustment for  
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11 280 covariates, and additionally, among participants with diabetes at baseline. Audiometry  
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14 281 to confirm hearing impairment was conducted by trained staff. Several limitations of the  
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17 282 study also need to be considered. First, information on noise exposure was not available  
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20 283 and thus noise information was not considered in the analyses. However, a previous  
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23 284 study reported that the relationship between diabetes and hearing impairment was  
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26 285 independent of this variable (37). Moreover, in the present study, HbA1c level was  
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29 286 associated with hearing impairment even after accounting for job type in a sensitivity  
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32 287 analysis. Second, information on ototoxic drug use, ear surgery, and ear infection was  
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35 288 not collected, and we were therefore unable to exclude cases of hearing impairment due  
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38 289 to these factors. Third, blood pressure was measured once, followed by a second  
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41 290 measurement if the first systolic blood pressure  $\geq 130$  mmHg systolic or diastolic blood  
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44 291 pressure  $\geq 85$  mmHg. All participants didn't have the same evaluation of blood pressure.  
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47 292 This may lead to misclassification of hypertension. Fourth, we did not account for  
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50 293 gender or smoking status in the association between HbA1c and hearing impairment for  
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53 294 participants with diabetes because of the small sample size. Fifth, the hearing test was  
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56 295 only conducted at 1 kHz and 4 kHz. Hearing impairment at other frequencies could not

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6 296 therefore be identified. Sixth, we cannot exclude the possibility of residual confounding  
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9 297 and confounding by unmeasured variables. Finally, the study participants were mainly  
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12 298 workers, and thus caution is required when generalizing our findings.

## 14 299 CONCLUSION

16  
17 300 We found the quadratic trend between HbA1c and the incidence of high frequency  
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20 301 hearing impairment in non-smokers. The trend between HbA1c and hearing impairment  
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23 302 remained even among those with diabetes. These findings indicate that diabetic-related  
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26 303 hearing impairment may be prevented with appropriate glycemetic control. These  
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29 304 findings warrant confirmation in interventional studies.

## 31 305 Abbreviations

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34 306 HbA1c: hemoglobin A1c; BMI: body mass index; HR: hazard ratio; CI: confidence  
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37 307 interval

## 39 308 Acknowledgements

40  
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42 309 The authors would like to thank Dr Nobuo Yanagisawa and Dr Takeshi Kawaguchi for  
43  
44  
45 310 coordinating the study.

## 48 311 Contributors

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51 312 SN, TaM and IK designed study and drafted the manuscript. SN, HHH, KaK, AN and  
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54 313 KeK performed the data analysis. MD collected and interpreted the data. All authors

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6 314 participated in interpretation of the findings, revised the paper critically for important  
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8 315 intellectual content and approved the final version to be published. YN and YM  
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11 316 provided administrative, technical and material support. SN and YN are guarantors.  
12  
13  
14 317 Funding  
15  
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17 318 This research was funded by All Japan Labor Welfare Foundation Research Fellowship.  
18  
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20 319 Competing interests  
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22  
23 320 None declared. SN is occupational physicians in the participating company.  
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26 321 Ethics approval  
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28 322 The research protocol was approved by the Ethics Committee of the Faculty of  
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31 323 Medicine, Toho University and the Ethics Committee of the National Center for Global  
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34 324 Health and Medicine.  
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37 325 Patient and public involvement  
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40 326 No patient were involved in setting the research question or the outcome measures,  
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43 327 planning for the design of the study. Detail has been removed from this case  
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46 328 description/these case descriptions to ensure anonymity. Patient consent was not  
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49 329 required for the study.  
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51 330 Data sharing statement  
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54 331 No additional data are available.  
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Table 1 Baseline characteristics of study participants according to HbA<sub>1c</sub> (n=202,975).

	HbA <sub>1c</sub> (%) (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)
<b>Men</b>								
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 (%) <sup>‡</sup>	2.3	0.07	0.10	0.4	4.6	22.4	41.1	37.3
BMI (kg/m <sup>2</sup> )*	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 (%) <sup>§</sup>	28	21	22	29	44	57	57	53
Dyslipidemia (%) <sup>†</sup>	39	29	33	41	54	59	60	65
<b>Women</b>								
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 (%) <sup>‡</sup>	1.2	0.05	0.03	0.1	2.5	17.4	38.2	47.5
BMI (kg/m <sup>2</sup> )*	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 (%) <sup>§</sup>	19	11	14	21	34	52	59	53
Dyslipidemia (%) <sup>†</sup>	22	13	16	24	39	54	61	59

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

\* Mean (SD)

<sup>†</sup> One go contains ~23g of ethanol.

<sup>‡</sup> Self-reported diagnosis of diabetes or receiving medication.

<sup>§</sup> Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication.

<sup>†</sup> 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 mmol/L) in women or receiving medication.

Table 2 Hazard ratio of hearing impairment according to baseline HbA<sub>1c</sub> (n = 202,975).

		HbA <sub>1c</sub> (%) (mmol/mol)							P for quadratic
		<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)	
<b>Low frequency</b>									
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
<b>High frequency</b>									
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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5 444 **Fig1.** The association between HbA1c and hearing impairment of high frequency stratified by smoking status.  
6 445 Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in  
7 446 non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or  
8 447  $\geq 30.0$  kg/m<sup>2</sup>), alcohol consumption (non-drinker, drinker consuming <1, 1 to <2, or  $\geq 2$  go of Japanese sake  
9 448 contains approximately 23g of ethanol), walking time (<60, or  $\geq 60$  min/day), self-reported diabetes, hypertension  
10 449 (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and  
11 450 hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving  
12 451 medication).

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5 **Fig 2.** Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline  
6 (n=10,154).  
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8 Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5,  
9 p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard  
10 ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex,  
11 body mass index (<18.5, 18.5-22.9, 23-29.9, or  $\geq 30.0$  kg/m<sup>2</sup>), smoking status (non-smoker, smoker consuming  $\leq 20$ ,  
12 or  $> 20$  cigarettes per day), alcohol consumption (non-drinker, drinker consuming  $<1$ ,  $1$  to  $<2$ , or  $\geq 2$  go of Japanese  
13 sake contains approximately 23g of ethanol), walking time (  $<60$ , or  $\geq 60$  min/day), hypertension (systolic blood  
14 pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride  
15 level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level  $<40$  mg/dL in men and  $<50$  mg/dL in women or  
16 receiving medication).  
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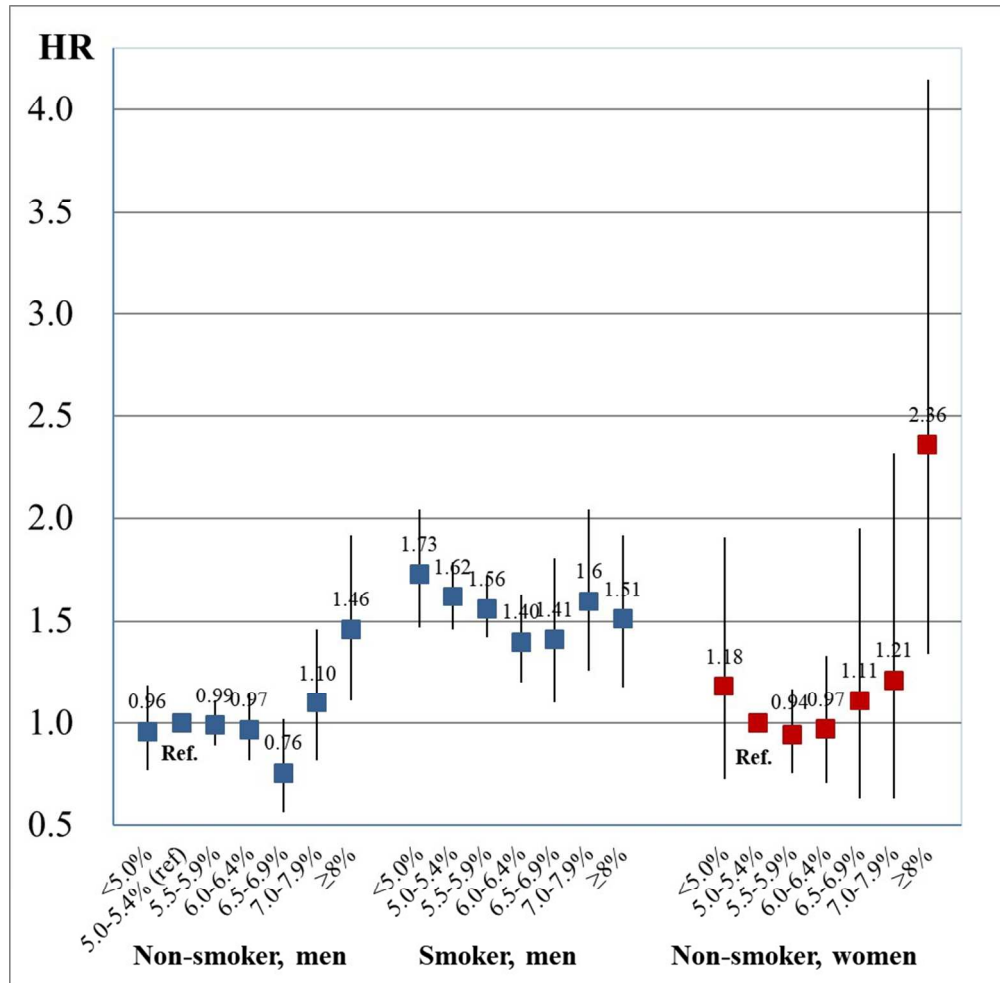


Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.

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/m<sup>2</sup>), 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)

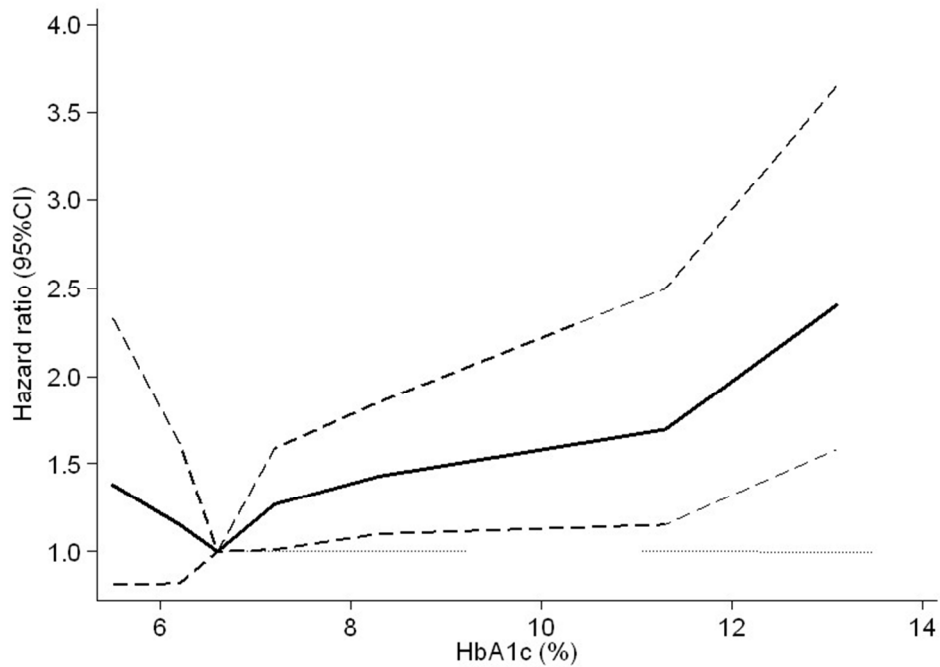


Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

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  $\geq 30.0$  kg/m<sup>2</sup>), smoking status (non-smoker, smoker consuming  $\leq 20$ , or  $> 20$  cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or  $\geq 2$  go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or  $\geq 60$  min/day), hypertension (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

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**Appendix 1. The association between baseline HbA<sub>1c</sub> and Incidence of high frequency hearing impairment (n=126,823).**

		HbA <sub>1c</sub> (%) (mmol/mol)							P for quadratic
		<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)	
<b>Men</b>	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
<b>Women</b>	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
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P1 Line1 P3 Line31, P4 Line51
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	P7 Line99-108
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 (b) Describe any methods used to examine subgroups and interactions	P10 Line157-193 P11 Line173-

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

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<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	P12 Line201-206
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	P12 Line200-206
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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-

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**Other information**


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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
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\*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](http://www.strobe-statement.org).



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023220.R1
Article Type:	Research
Date Submitted by the Author:	15-Jun-2018
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Ear, nose and throat/otolaryngology, Epidemiology
Keywords:	EPIDEMIOLGY, Diabetes & endocrinology < INTERNAL MEDICINE, OCCUPATIONAL & INDUSTRIAL MEDICINE, Audiology < OTOLARYNGOLOGY

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1 **Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large**

2 **occupational health check-up data of Japan**

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39 31 Word count 3,091

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42 32 Tables 2

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6 34 **Objectives** The aim of this study was to determine whether hemoglobin A1c (HbA1c)  
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8 35 level is associated with the incidence of hearing impairment accounting for smoking  
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11 36 status and diabetic condition at baseline.

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14 37 **Methods** Participants were 131,689 men and 71,286 women aged 30-65 years and free  
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17 38 of hearing impairment at baseline (2008) who attended annual health check-ups from  
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20 39 2008 to 2015. We defined low frequency hearing impairment at a hearing threshold >30  
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23 40 dB at 1 kHz and high frequency at >40 dB at 4 kHz in the better ear in pure-tone  
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26 41 audiometric tests. HbA1c was categorized into 7 categories. The association between  
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29 42 HbA1c and hearing impairment was assessed using the Cox proportional hazards  
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32 43 model.

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34 44 **Results** On 5 years' mean follow-up, high HbA1c was associated with high frequency  
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37 45 hearing impairment. In non-smokers, HbA1c  $\geq 8.0\%$  was associated with high frequency  
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40 46 hearing impairment, with a multivariable hazard ratio (95% confidence interval)  
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43 47 compared with HbA1c 5.0-5.4% of 1.46 (1.10-1.94) in men and 2.15 (1.13-4.10) in  
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46 48 women. There was no significant association between HbA1c and hearing impairment  
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49 49 in smokers. A J-shaped association between HbA1c and high frequency hearing  
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52 50 impairment was observed for participants with diabetes at baseline. HbA1c was not  
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55 51 associated with low frequency hearing impairment among any participants.

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6 52 **Conclusions** HbA1c  $\geq 8.0\%$  of non-smokers and  $\geq 7.3\%$  of participants with diabetes  
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9 53 was associated with high frequency hearing impairment. These findings indicate that  
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11 54 appropriate glycemic control may prevent diabetic-related hearing impairment.  
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17 56 **Strengths and limitations of this study**  
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20 57 ▪ This study included a large number of participants, accounting for gender and smoking  
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23 58 status.

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25 59 ▪ To determine whether HbA1c was associated with hearing impairment among  
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28 60 participants with diabetes at baseline.

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31 61 ▪ Information on noise exposure, ototoxic drug use, ear surgery, and ear infection was  
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34 62 not obtained.  
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6 **64 BACKGROUND**

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9 **65** Patients with hearing impairment experience a range of complications, including  
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11 **66** impaired quality of life, dementia, depression, loneliness, poor self-esteem and  
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14 **67** functional disability (1-4). These complications have made this condition a social and  
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17 **68** economic problem worldwide. More than 5% of the world population has hearing  
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20 **69** impairment, and this is expected to increase with the aging of the population (5).  
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23 **70** Although this bleak picture points to the importance of identifying preventable risk  
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26 **71** factors for hearing impairment, such studies are in fact scarce.  
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29 **72** Emerging evidence suggests that diabetes mellitus may be a risk factor for hearing  
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32 **73** impairment. Meta-analyses of 13 cross-sectional studies showed that subjects with  
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35 **74** diabetes had a 2-fold-increased risk of developing hearing impairment (odds ratio 2.15,  
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38 **75** 95%CI 1.72-2.68) (6). Diabetic hearing impairment is hypothesized to be due to  
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41 **76** microvascular complications (7, 8). Diabetic hearing impairment may thus be prevented  
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44 **77** by appropriate glyceic control, which has been shown to be effective for other  
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47 **78** microvascular complications of diabetes, such as retinopathy, nephropathy and  
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50 **79** neuropathy (9-12). Three studies have reported the association between hearing  
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53 **80** impairment and hemoglobin A1c (HbA1c), an indicator for glyceic control (13-15).  
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56 **81** One of these reported a positive dose-relationship between HbA1c and hearing  
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6 82 impairment as defined using a pure-tone average threshold of mainly low frequencies  
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9 83 (15), while the other two reported that HbA1c was positively associated with high  
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11 84 frequency hearing impairment (13, 14). Nevertheless, no study has yet reported the  
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14 85 precise shape of the dose-relationship between HbA1c and high frequency hearing  
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17 86 impairment. Furthermore, no study has yet investigated whether HbA1c is associated  
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20 87 with hearing impairment among those with diabetes.  
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23 88 In Japan, a pure-tone audiometric test is mandatory in annual occupational health  
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26 89 check-ups (16). The large sample size this affords has enabled us to investigate the  
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29 90 dose-response relationship between HbA1c and hearing impairment, while accounting  
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32 91 for well-known risk factors of hearing impairment such as gender and smoking (17, 18).  
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35 92 The present study had two aims. The first aim was to investigate the association  
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38 93 between HbA1c and the incidence of hearing impairment using a large dataset from  
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41 94 annual occupational health check-ups in Japan, accounting for gender and smoking  
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44 95 status. The second aim was to determine whether HbA1c was associated with hearing  
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47 96 impairment among participants with diabetes.  
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## 98 **METHODS**

### 99 **Study population**



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6 100 The present study was conducted using data from annual health check-ups of Japanese  
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9 101 workers. The All Japan Labor Welfare Foundation, a health service provider with  
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11 102 centers in Tokyo, Aomori, Nagano, Yamagata, Ibaraki, Gunma and Nagoya provided the  
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14 103 data from April 2008 through Dec 2015, allowing a maximum of 7 years of follow-up.  
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17 104 In Japan, annual health check-ups are mandatory for all employees and include a  
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20 105 hearing test under the Industrial Safety and Health Act. Nearly all employees attend a  
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23 106 health check-up every year. Participants were mainly Japanese employees but also  
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26 107 included a small number of their dependents, employers and foreign workers.  
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28 108 A total of 312,512 participants aged 30-65 years underwent a hearing test and HbA1c  
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31 109 test at baseline (between Apr 2008 and Mar 2009). Of these, we excluded participants  
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34 110 with hearing impairment at baseline (n=51,489). Given that diabetic patients with  
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37 111 complications may receive more intensive treatments, which may bias the association  
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40 112 between HbA1c and hearing impairment, we excluded participants with cardiovascular  
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43 113 disease and stroke (n=913). We further excluded participants who did not attend any  
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46 114 subsequent health examinations or hearing tests (n=48,618). After further exclusion of  
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49 115 8,517 participants with missing information on covariates (5,011 for smoking status,  
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51  
52 116 5,152 for alcohol consumption, 1,815 for physical activity data, 5 for body mass index  
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55 117 (BMI), 9 for hypertension and 9 for dyslipidemia data; some participants had missing  
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6 118 data for more than one parameter), leaving 202,975 participants (131,689 men and  
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8 119 71,286 women) for analysis.

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11 120 Ethics

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14 121 We obtained written informed consent from each participant who attended the health  
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17 122 check-up after April 2013. Before March 2013, we disclosed the purpose of our study  
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20 123 by posters and the participants had the opportunity to refuse the use of their data for the  
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23 124 study. This procedure conforms to the Japanese Ethical Guidelines for Medical and  
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26 125 Health Research Involving Human Subjects, where the obtaining consent may be  
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29 126 simplified for observational studies using existing data. The research protocol including  
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32 127 consent procedure was approved by the Ethics Committee of the Faculty of Medicine,  
33  
34 128 Toho University (No. 25017 and No.A16130) and the Ethics Committee of the National  
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36  
37 129 Center for Global Health and Medicine (No. NCGM-G-001254-02).

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40 130 Ascertainment of hearing impairment

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42 131 Trained staff performed pure-tone air-conduction audiometry using an audiometer  
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45 132 (AA-57, RION Inc., Tokyo, Japan). Low frequency hearing impairment was defined as  
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48 133 failure to hear a pure-tone signal of 30dB at 1 kHz in the better ear, and high frequency  
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51 134 hearing impairment as failure to hear a pure-tone signal of 40dB at 4 kHz in the better  
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54 135 ear. These thresholds are recommended for use in annual health check-ups by Ministry

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6 136 of Health, Labor and Welfare in Japan (16). Onset of hearing impairment was defined as  
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9 137 the day of the health check-up on which hearing impairment was first detected.  
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11 138 Data collection and measurements at baseline (between Apr 2008 and Mar 2009)  
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14 139 We used a self-administered questionnaire developed by the Ministry of Health, Labor  
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17 140 and Welfare for a specific health examination, namely the national health checkup  
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20 141 system focused on metabolic syndrome (19), to assess medical history, regular physical  
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23 142 activity (walking time  $<60$  min/day or  $\geq 60$  min/day), smoking status (non-smoker, daily  
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26 143 smoker  $\leq 20$  cigarettes/day or  $>20$  cigarettes/day), alcohol consumption (non-drinker,  $<1$   
27  
28  
29 144 *go*, 1 to  $<2$  *go* or  $\geq 2$  *go*/day; one *go* of sake, a traditional Japanese beverage, is equal to  
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32 145 about 180 mL of 10-14% ethanol and contains about 23 g of ethanol) (20), and  
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35 146 self-reported diabetes (treatments with anti-diabetic medication or a self-reported  
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38 147 history of diabetes: yes or no). Job type was categorized as professional job,  
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41 148 management, office job, sales, service, telegraph, manufacturing, transportation and  
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44 149 other. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body  
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47 150 mass index (BMI) was calculated as the weight in kilograms divided by the square of  
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50 151 height in metres and categorized into 4 groups ( $<18.5$ , 18.5-22.9, 23-29.9,  $\geq 30$ kg/m<sup>2</sup>).  
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53 152 Blood pressure was measured in the sitting position using an automated  
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56 153 sphygmomanometer (HEM-907, Omron, Kyoto, Japan). Participants with high blood

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6 154 pressure ( $\geq 130$  mmHg systolic or  $\geq 85$  mmHg diastolic) received a second measurement  
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9 155 and the average was used for the analysis. Hypertension was defined by  $\geq 140$  mmHg  
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11 156 systolic,  $\geq 90$  mmHg diastolic or the use of medication for hypertension. A venous blood  
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14 157 sample was collected and stored in a cooler at 4 °C for transportation to an external  
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17 158 laboratory (SRL, Tokyo, Japan). Triglyceride level was measured using an enzymatic  
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20 159 colorimetric test and high-density lipoprotein cholesterol (HDL-C) was determined  
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23 160 using a direct method. Dyslipidemia was defined by triglyceride  $\geq 150$  mg/dL (1.7  
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25  
26 161 mmol/L) in men and women, HDL-C  $< 40$  mg/dL (1.04 mmol/L) in men and  $< 50$  mg/dL  
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28  
29 162 (1.3 mmol/L) in women or use of medication for dyslipidemia. HbA1c was measured by  
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32 163 latex agglutination turbidimetry and converted to the National Glycohemoglobin  
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35 164 Standardization Program equivalent value (%) using the formula below, according to the  
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38 165 Japan Diabetes Society statement (21) :  
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40 166  $\text{HbA1c (\%)} = 1.02 \times \text{HbA1c (Japan Diabetes Society) (\%)} + 0.25\%$   
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43 167 Diabetes was defined as  $\text{FPG} \geq 126$  mg/dL,  $\text{HbA1c} \geq 6.5\%$ , or self-reported diabetes.  
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46 168 Statistical analysis  
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49 169 Participants were divided into 7 groups according to their HbA1c level at baseline  
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52 170 [ $< 5.0\%$  (31 mmol/mol), 5.0-5.4% (31-36 mmol/mol), 5.5-5.9% (37-41 mmol/mol),  
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55 171 6.0-6.4% (42-46 mmol/mol), 6.5-6.9% (48-52 mmol/mol), 7.0-7.9% (53-63 mmol/mol),  
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6 172  $\geq 8.0\%$  (64 mmol/mol)]. The HbA1c group specific baseline characteristics of  
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9 173 participants were described as means (SD) for continuous variables and percentages for  
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11 174 categorical variables. Person-years was calculated from baseline to the onset of hearing  
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14 175 impairment, or the date of the last health check-up through Dec 2015 (whichever  
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17 176 occurred first). Crude incident rates of hearing impairment were shown in events per  
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20 177 1000 person-years. Survival analyses were performed using Cox regression to estimate  
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23 178 the hazard ratio (HR) with 95% confidence interval (CI) for the incidence of hearing  
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26 179 impairment across HbA1c categories, with 5.0-5.4% (31-36mmol/mol) as the reference  
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29 180 value. The analyses were stratified by sex because the interaction between hearing  
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31 181 impairments and sex was significant ( $p$  for interaction  $<0.001$ ). Age-adjusted model  
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34 182 (model 1) and multiple-adjusted model (model 2), which included alcohol consumption,  
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37 183 physical activity, BMI, hypertension, dyslipidemia, self-reported diabetes and smoking  
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40 184 status were used for the analysis. Although smoking status itself was related to hearing  
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43 185 impairment in this study, the association between HbA1c and hearing impairment  
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46 186 differed according to smoking status ( $p$  for interaction  $<0.001$ ). We therefore  
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49 187 additionally performed analyses according to combined HbA1c (7 groups) and smoking  
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52 188 status (non-smoker and current smoker), by considering HbA1c 5.0-5.4%  
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54 189 (31-36mmol/mol) and non-smoker as the reference category. We did not analyze  
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6 190 women's smokers because of the small number of cases. To assess whether control of  
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9 191 HbA1c would reduce the incidence of hearing impairment in those with diabetes, we  
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11 192 elucidated the shape of the relationship between HbA1c and high frequency hearing  
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14 193 impairment among those with diabetes. We fitted restricted cubic splines models with  
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17 194 seven knots placed at the 1th, 5th, 25th, 50th, 75th, 95th, and 99th centiles as reference  
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20 195 values of HbA1c 6.6% (25th) (22). The HRs were adjusted for alcohol consumption,  
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23 196 physical activity, BMI, hypertension, dyslipidemia and smoking status. As a sensitivity  
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26 197 analysis, we further adjusted for job type in the main analyses (model 2) among  
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29 198 participants with this information (n=126,823). We tested the proportional hazards  
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32 199 assumption using Schoenfeld residuals. We found no significant deviations for any  
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35 200 covariate. P value of two-tailed test <0.05 was considered statistically significant. Trend  
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38 201 association was assessed by assigning ordinal numbers (0–6) to the HbA1c categories.  
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41 202 We calculated the p for the quadratic trend because it was a better fit for the data than  
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44 203 the simple linear model. All statistical analyses were performed using Stata version 12.1  
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47 204 (StataCorp, College Station, Texas, USA).

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51 206 **RESULTS**

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6 207 Baseline characteristics by category of HbA1c are shown in Table 1. The mean age of  
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9 208 participants was 45 years for men and 47 years for women. Participants who had higher  
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11 209 HbA1c tended to be non-drinkers and to have higher BMI, hypertension, and  
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14 210 dyslipidemia in both men and women. Male participants with higher HbA1c tended to  
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17 211 be smokers consuming > 20 cigarettes per day.  
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20 212 In men, 4,621 developed high frequency hearing impairment with 661,937 person-years  
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23 213 (mean duration of follow-up was 5.0 years) and 1,311 developed low frequency hearing  
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26 214 impairment with 670,153 person-years (5.1 years). In women, 582 developed high  
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29 215 frequency hearing impairment with 345,312 person-years (4.8 years) and 1,207  
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32 216 developed low frequency hearing impairment with 344,057 person-years (4.8 years).  
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34 217 Table 2 shows the association between HbA1c and the incidence of hearing impairment.  
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37 218 In the multivariable-adjusted model, HbA1c showed a quadratic trend with the  
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40 219 incidence of high frequency hearing impairment in men (p for quadratic=0.007), and a  
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43 220 statistically marginal association in women (p for quadratic=0.08). HbA1c was not  
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46 221 associated with low frequency hearing impairment. Figure 1 shows the association  
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49 222 between HbA1c and high frequency hearing impairment with accounting for smoking  
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52 223 status [the interaction between HbA1c and smoking status (p for interaction <0.001)].  
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55 224 Compared to non-smokers with HbA1c 5.0-5.4% (31-36mmol/mol), non-smokers with  
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6 225 HbA1c  $\geq$ 8.0% (64 mmol/mol) showed an association with hearing impairment [HR  
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8 226 (95%CI) of 1.46 (1.11-1.92) in men and 2.36 (1.34-4.15) in women]. Although smokers  
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11 227 had higher HRs of hearing impairment than non-smokers, HbA1c level was not  
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14 228 associated with hearing impairment among smokers. Additional adjustments for job  
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17 229 type did not affect the results (Appendix 1).  
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20 230 Figure 2 shows the spline regression model of high frequency hearing impairment at  
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23 231 various HbA1c levels against a reference HbA1c level of 6.6% in participants with  
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26 232 diabetes at baseline (n=10,154). The relationship between HbA1c and the incidence of  
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29 233 hearing impairment was J-shaped, with the significant increase of HR for HbA1c $\geq$ 7.2%.  
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## 34 235 **DISCUSSION**

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37 236 In this study, we found a quadratic trend between HbA1c and the incidence of  
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40 237 high frequency hearing impairment. In particular, HbA1c concentrations over 8.0% (64  
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43 238 mmol/mol) were associated with high frequency hearing impairment among  
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46 239 non-smokers. A J-shaped association between HbA1c and high frequency hearing  
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49 240 impairment was observed among participants with diabetes at baseline. Our findings  
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52 241 indicate that appropriate glycemic control may prevent the incidence of diabetic hearing  
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55 242 impairment.  
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6 243 Our finding of a quadratic trend between HbA1c and hearing impairment is  
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9 244 supported by the results of two longitudinal studies. (13, 15) One of these reported an  
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11 245 odds ratio (95% CI) of high frequency hearing impairment per 1.0% increase in HbA1c  
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14 246 of 1.52 (1.03 to 2.23), albeit no statistical association between the three categories of  
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17 247 HbA1c and high frequency hearing impairment (13). The second reported that HbA1c  
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20 248 was positively associated with average hearing threshold, mainly among low  
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23 249 frequencies (15). The present study provides novel evidence that an HbA1c of 8.0% (64  
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25 250 mmol/mol) or above is associated with increased risk of high frequency hearing  
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28 251 impairment in non-smokers. Our findings are consistent with the work of Cruickshanks  
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31 252 et al., who reported that poor glycemic control, defined by a glycosylated hemoglobin  
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34 253 level, was associated with hearing impairment (23).

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37 254 Additionally, we found that the J-shaped association between HbA1c and  
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40 255 hearing impairment remained even among participants with diabetes at baseline. This  
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43 256 result suggests that proper glycemic control may prevent diabetic-related hearing  
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46 257 impairment even in those with diabetes. Previous studies have also reported a J-shaped  
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49 258 association between HbA1c and diabetics complications, and noted that hypoglycemia  
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51 259 might increase diabetic complications (24-26). More research is needed to determine a  
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6 260 suitable HbA1c level for glycaemic targeting to prevent hearing impairment in diabetic  
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9 261 management.

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11 262 We found that high frequency hearing impairment has a quadratic trend with  
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14 263 HbA1c among non-smokers but not smokers. Previous studies have reported an adverse  
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17 264 effect of smoking cigarettes on hearing impairment (23, 27, 28). It is plausible that the  
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20 265 effect of smoking cigarettes may be stronger than HbA1c and might mask the effect of  
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23 266 HbA1c. Further research is needed to confirm the joint effect of smoking and HbA1c on  
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26 267 hearing impairment.

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28 268 The pathophysiology underlying high-HbA1c-associated hearing impairment is  
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31 269 unclear, which allows for speculation. One possible explanation is that  
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34 270 hyperglycemia-related microvascular complications lead to thickening of the cochlea  
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37 271 and vestibulopathy, and result in hearing impairment (7, 8, 29-33). Diabetic-related  
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40 272 hearing impairment has been mainly observed at high frequencies, suggesting that high  
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43 273 frequency-specific areas of the cochlea may be more fragile to ischemic changes due to  
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46 274 microvascular complications (34-38). This mechanism is supported by the J-shaped  
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49 275 association between HbA1c and hearing impairment observed in the present study, since  
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52 276 previous studies also reported a J-shaped-association between HbA1c and diabetic  
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54 277 vascular complications (39, 40). Further studies to confirm this idea are required.  
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6 278 This study has several strengths. The large dataset allowed us to investigate the  
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9 279 association between HbA1c and hearing impairment with comprehensive adjustment for  
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12 280 covariates, and additionally, among participants with diabetes at baseline. Audiometry  
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15 281 to confirm hearing impairment was conducted by trained staff. Several limitations of the  
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18 282 study also need to be considered. First, though noise exposure is an important risk factor  
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21 283 on hearing impairment (41, 42), information on noise exposure was not available and  
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24 284 thus noise information was not considered in the analyses. The present study thus might  
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27 285 include the cofounding influence of noise exposure. However, a previous study reported  
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30 286 that the relationship between diabetes and hearing impairment was independent of this  
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33 287 variable (37). Moreover, in the present study, HbA1c level was associated with hearing  
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36 288 impairment even after accounting for job type in a sensitivity analysis. Second,  
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39 289 information on ototoxic drug use, ear surgery, and ear infection was not collected, and  
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42 290 we were therefore unable to exclude cases of hearing impairment due to these factors.  
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45 291 Third, blood pressure was measured once, followed by a second measurement if the first  
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48 292 systolic blood pressure  $\geq 130$  mmHg systolic or diastolic blood pressure  $\geq 85$  mmHg. All  
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51 293 participants didn't have the same evaluation of blood pressure. This may lead to  
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54 294 misclassification of hypertension. Fourth, we did not account for gender or smoking  
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57 295 status in the association between HbA1c and hearing impairment for participants with

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6 296 diabetes because of the small sample size. Fifth, the hearing test was only conducted at  
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9 297 1 kHz and 4 kHz. Hearing impairment at other frequencies could not therefore be  
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11 298 identified. Sixth, we cannot exclude the possibility of residual confounding and  
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14 299 confounding by unmeasured variables. Finally, the study participants were mainly  
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17 300 workers, and thus caution is required when generalizing our findings.  
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## 20 301 **CONCLUSION**

21  
22 302 We found the quadratic trend between HbA1c and the incidence of high  
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25 303 frequency hearing impairment in non-smokers. The trend between HbA1c and hearing  
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28 304 impairment remained even among those with diabetes. These findings indicate that  
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31 305 diabetic-related hearing impairment may be prevented with appropriate glycemic  
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34 306 control. These findings warrant confirmation in interventional studies.  
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## 36 307 **Abbreviations**

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39 308 HbA1c: hemoglobin A1c; BMI: body mass index; HR: hazard ratio; CI: confidence  
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42 309 interval  
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## 44 310 **Acknowledgements**

45  
46  
47  
48 311 The authors would like to thank Dr Nobuo Yanagisawa and Dr Takeshi Kawaguchi for  
49  
50  
51 312 coordinating the study.  
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## 53 313 **Contributors**

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6 314 SN, TaM and IK designed study and drafted the manuscript. SN, HHH, KaK, AN and

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8 315 KeK performed the data analysis. MD collected and interpreted the data. All authors

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11 316 participated in interpretation of the findings, revised the paper critically for important

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14 317 intellectual content and approved the final version to be published. YN and YM

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16  
17 318 provided administrative, technical and material support. SN and YN are guarantors.

18  
19  
20 319 Funding

21  
22  
23 320 This research was funded by All Japan Labor Welfare Foundation Research Fellowship.

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26 321 Competing interests

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29 322 None declared. SN is occupational physicians in the participating company.

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32 323 Ethics approval

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35 324 The research protocol was approved by the Ethics Committee of the Faculty of

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38 325 Medicine, Toho University and the Ethics Committee of the National Center for Global

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41 326 Health and Medicine.

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44 327 Patient and public involvement

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47 328 No patient were involved in setting the research question or the outcome measures,

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50 329 planning for the design of the study. Detail has been removed from this case

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53 330 description/these case descriptions to ensure anonymity. Patient consent was not

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56 331 required for the study.

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332 Data sharing statement  
333 No additional data are available.  
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For peer review only

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Table 1 Baseline characteristics of study participants according to HbA<sub>1c</sub> (n=202,975).

	HbA <sub>1c</sub> (%) (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)
<b>Men</b>								
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 <sup>†</sup>	35	32	35	36	34	34	30	32
Drinker 1 to <2 go/day <sup>†</sup>	26	30	27	25	25	25	26	22
Drinker ≥2 go/day <sup>†</sup>	12	19	13	10	10	11	11	10
Self-reported diabetes (%) <sup>‡</sup>	2.3	0.07	0.10	0.4	4.6	22.4	41.1	37.3
BMI (kg/m <sup>2</sup> )*	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 (%) <sup>§</sup>	28	21	22	29	44	57	57	53
Dyslipidemia (%) <sup>  </sup>	39	29	33	41	54	59	60	65
<b>Women</b>								
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 <sup>†</sup>	31	36	34	29	26	22	22	19
Drinker 1 to <2 go/day <sup>†</sup>	6.8	14.4	7.8	5.0	3.8	3.9	3.7	2.7
Drinker ≥2 go/day <sup>†</sup>	1.7	5.3	1.9	1.0	0.5	0.6	0.5	0.7
Self-reported diabetes (%) <sup>‡</sup>	1.2	0.05	0.03	0.1	2.5	17.4	38.2	47.5
BMI (kg/m <sup>2</sup> )*	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 (%) <sup>§</sup>	19	11	14	21	34	52	59	53
Dyslipidemia (%) <sup>  </sup>	22	13	16	24	39	54	61	59

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

\* Mean (SD)

<sup>†</sup> One go contains ~23g of ethanol.

<sup>‡</sup> Self-reported diagnosis of diabetes or receiving medication.

<sup>§</sup> Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication.

<sup>||</sup> 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 mmol/L) in women or receiving medication.

Table 2 Hazard ratio of hearing impairment according to baseline HbA<sub>1c</sub> (n = 202,975).

		HbA <sub>1c</sub> (%) (mmol/mol)							P for quadratic
		<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)	
<b>Low frequency</b>									
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
<b>High frequency</b>									
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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5 452 **Fig1.** The association between HbA1c and hearing impairment of high frequency stratified by smoking status.  
6 453 Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in  
7 454 non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or  
8 455  $\geq 30.0$  kg/m<sup>2</sup>), alcohol consumption (non-drinker, drinker consuming <1, 1 to <2, or  $\geq 2$  go of Japanese sake  
9 456 contains approximately 23g of ethanol), walking time (<60, or  $\geq 60$  min/day), self-reported diabetes, hypertension  
10 457 (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and  
11 458 hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving  
12 459 medication).

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5 **Fig 2.** Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline  
6 (n=10,154).  
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8 Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5,  
9 p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard  
10 ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex,  
11 body mass index (<18.5, 18.5-22.9, 23-29.9, or  $\geq 30.0$  kg/m<sup>2</sup>), smoking status (non-smoker, smoker consuming  $\leq 20$ ,  
12 or  $> 20$  cigarettes per day), alcohol consumption (non-drinker, drinker consuming  $<1$ ,  $1$  to  $< 2$ , or  $\geq 2$  go of Japanese  
13 sake contains approximately 23g of ethanol), walking time (  $<60$ , or  $\geq 60$  min/day), hypertension (systolic blood  
14 pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride  
15 level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level  $<40$  mg/dL in men and  $<50$  mg/dL in women or  
16 receiving medication).  
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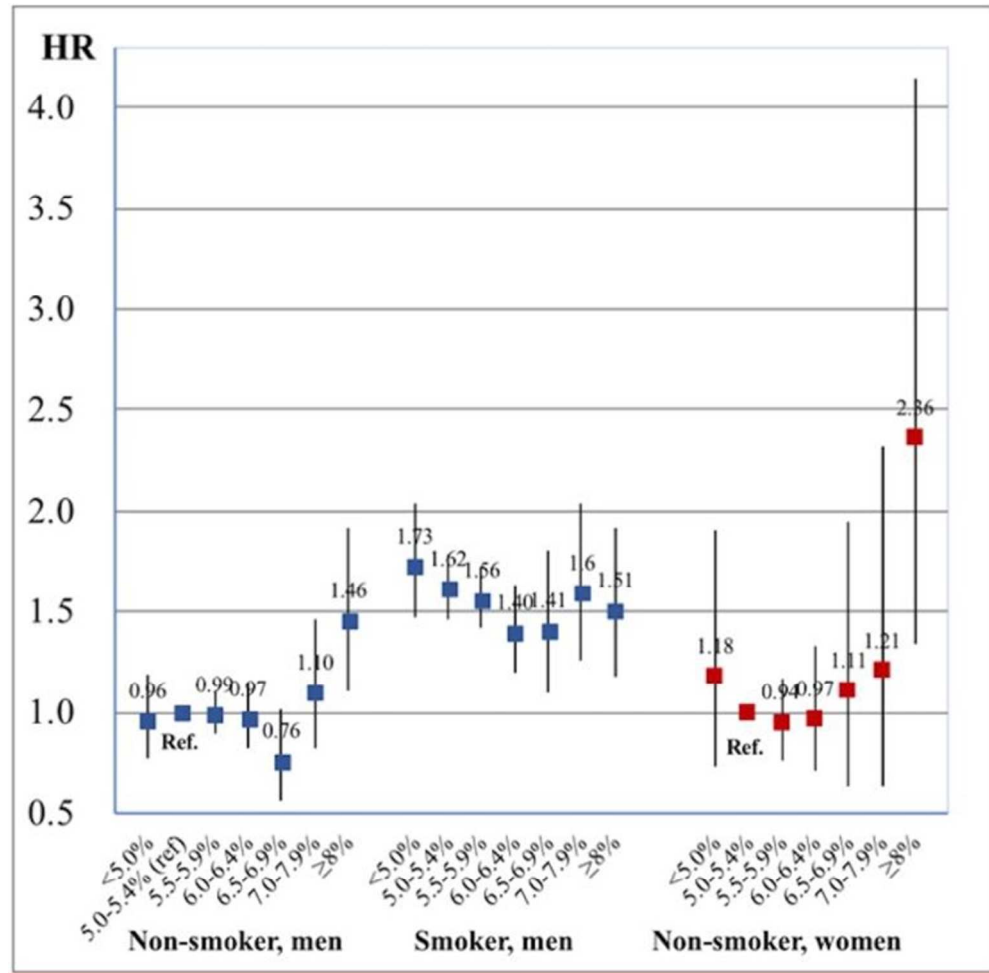


Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.

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  $\geq 30.0$  kg/m<sup>2</sup>), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or  $\geq 2$  go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or  $\geq 60$  min/day), self-reported diabetes, hypertension (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving medication).

203x197mm (96 x 96 DPI)

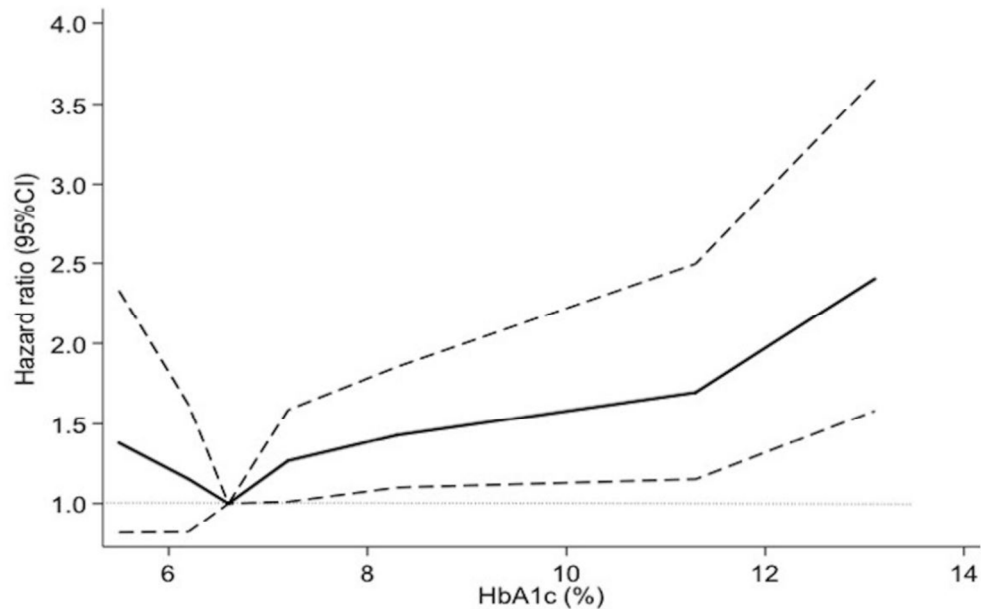


Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

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  $\geq 30.0$  kg/m<sup>2</sup>), smoking status (non-smoker, smoker consuming  $\leq 20$ , or  $> 20$  cigarettes per day), alcohol consumption (non-drinker, drinker consuming <1, 1 to < 2, or  $\geq 2$  go of Japanese sake contains approximately 23g of ethanol), walking time (<60, or  $\geq 60$  min/day), hypertension (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women or receiving medication).

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Appendix 1. The association between baseline HbA<sub>1c</sub> and Incidence of high frequency hearing impairment (n=126,823).

		HbA <sub>1c</sub> (%) (mmol/mol)							P for quadratic
		<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)	
<b>Men</b>	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
<b>Women</b>	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.

1

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

	Item No	Recommendation	Page number
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P1 Line1 P3 Line31, P4 Line51
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	P7 Line99-108
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 (b) Describe any methods used to examine subgroups and interactions	P10 Line157-193 P11 Line173-

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(c) Explain how missing data were addressed

P7

Line105-

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(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

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(e) Describe any sensitivity analyses

P12

Line185-

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Continued on next page

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<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	P12 Line201-206
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	P12 Line200-206
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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-

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**Other information**


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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
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\*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](http://www.strobe-statement.org).



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023220.R2
Article Type:	Research
Date Submitted by the Author:	31-Jul-2018
Complete List of Authors:	Nagahama, Satsue; Toho University Graduate School of Medicine, Department of Environmental and Occupational Health; All Japan Labor Welfare Foundation, Division of Occupational Health and Promotion Kashino, Ikuko; National Center for Global Health and Medicine, Department of Epidemiology and Prevention, Center for Clinical Sciences Hu, Huanhuan; National Center for Global Health and Medicine, Department of Epidemiology and Prevention, Center for Clinical Sciences Nanri, Akiko; Fukuoka Women's University, Department of Food and Health Sciences International College of Arts and Sciences Kurotani, Kayo; National Institutes of Biomedical Innovation, Health and Nutrition, National Institute of Health and Nutrition, Department of Nutritional Epidemiology and Shokuiku Kuwahara, Keisuke; Teikyo University, Graduate School of Public Health; National Center for Global Health and Medicine, Department of Epidemiology and Prevention, Center for Clinical Sciences Dan, Masashi; All Japan Labor Welfare Foundation, Michikawa, Takehiro; National Institute for Environmental Studies, Environmental Epidemiology Section, Center for Environmental Health Sciences Akter, Shamima; National Center for Global Health and Medicine, Department of Epidemiology and Prevention, Center for Clinical Sciences Mizoue, Tetsuya; National Center for Global Health and Medicine, Department of Epidemiology and Prevention, Center for Clinical Sciences Murakami, Yoshitaka ; Toho University Graduate School of Medicine, Department of Medical statistics Nishiwaki, Yuji; Toho University Graduate School of Medicine, Department of Environmental and Occupational Health
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Ear, nose and throat/otolaryngology, Epidemiology
Keywords:	EPIDEMOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, OCCUPATIONAL & INDUSTRIAL MEDICINE, Audiology < OTOLARYNGOLOGY

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Manuscripts

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1 **Hemoglobin A1c and Hearing Impairment: longitudinal analysis using a large**

2 **occupational health check-up data of Japan**

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39 31 Word count 3,091

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42 32 Tables 2

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6 34 **Objectives** The aim of this study was to determine whether hemoglobin A1c (HbA1c)  
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8 35 level is associated with the incidence of hearing impairment accounting for smoking  
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11 36 status and diabetic condition at baseline.

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14 37 **Methods** Participants were 131,689 men and 71,286 women aged 30-65 years and free  
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17 38 of hearing impairment at baseline (2008) who attended Japanese occupational annual  
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20 39 health check-ups from 2008 to 2015. We defined low frequency hearing impairment at a  
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22  
23 40 hearing threshold >30 dB at 1 kHz and high frequency at >40 dB at 4 kHz in the better  
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26 41 ear in pure-tone audiometric tests. HbA1c was categorized into 7 categories. The  
27  
28  
29 42 association between HbA1c and hearing impairment was assessed using the Cox  
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31  
32 43 proportional hazards model.

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34 44 **Results** On 5 years' mean follow-up, high HbA1c was associated with high frequency  
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36  
37 45 hearing impairment. In non-smokers, HbA1c  $\geq 8.0\%$  was associated with high frequency  
38  
39  
40 46 hearing impairment, with a multivariable hazard ratio (95% confidence interval)  
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43 47 compared with HbA1c 5.0-5.4% of 1.46 (1.10-1.94) in men and 2.15 (1.13-4.10) in  
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45  
46 48 women. There was no significant association between HbA1c and hearing impairment  
47  
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49 49 in smokers. A J-shaped association between HbA1c and high frequency hearing  
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52 50 impairment was observed for participants with diabetes at baseline. HbA1c was not  
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55 51 associated

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6 52 with low frequency hearing impairment among any participants.  
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8 53 **Conclusions** HbA1c  $\geq 8.0\%$  of non-smokers and  $\geq 7.3\%$  of participants with diabetes  
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11 54 was associated with high frequency hearing impairment. These findings indicate that  
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14 55 appropriate glycemic control may prevent diabetic-related hearing impairment.  
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20 57 **Strengths and limitations of this study**  
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23 58 ▪ This study included a large number of participants, accounting for gender and smoking  
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25 59 status.  
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28 60 ▪ A median follow-up period was 5 years.  
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31 61 ▪ This study findings are limited to workers in Japan.  
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33  
34 62 ▪ We investigated whether HbA1c was associated with hearing impairment among  
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36 63 participants with diabetes at baseline.  
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39 64 ▪ Information on noise exposure, ototoxic drug use, ear surgery, and ear infection was  
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41 65 not obtained.  
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6 **66 BACKGROUND**

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9 **67** Patients with hearing impairment experience a range of complications, including  
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11 **68** impaired quality of life, dementia, depression, loneliness, poor self-esteem and  
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14 **69** functional disability (1-4). These complications have made this condition a social and  
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17 **70** economic problem worldwide. More than 5% of the world population has hearing  
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20 **71** impairment, and this is expected to increase with the aging of the population (5).  
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23 **72** Although this bleak picture points to the importance of identifying preventable risk  
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26 **73** factors for hearing impairment, such studies are in fact scarce.  
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29 **74** Emerging evidence suggests that diabetes mellitus may be a risk factor for hearing  
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32 **75** impairment. Meta-analyses of 13 cross-sectional studies showed that subjects with  
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35 **76** diabetes had a 2-fold-increased risk of developing hearing impairment (odds ratio 2.15,  
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38 **77** 95%CI 1.72-2.68) (6). Diabetic hearing impairment is hypothesized to be due to  
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41 **78** microvascular complications (7, 8). Diabetic hearing impairment may thus be prevented  
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44 **79** by appropriate glycaemic control, which has been shown to be effective for other  
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47 **80** microvascular complications of diabetes, such as retinopathy, nephropathy and  
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50 **81** neuropathy (9-12). Three studies have reported the association between hearing  
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53 **82** impairment and hemoglobin A1c (HbA1c), an indicator for glycaemic control (13-15).  
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56 **83** One of these reported a positive dose-relationship between HbA1c and hearing

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6 84 impairment as defined using a pure-tone average threshold of mainly low frequencies  
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9 85 (15), while the other two reported that HbA1c was positively associated with high  
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11 86 frequency hearing impairment (13, 14). Nevertheless, no study has yet reported the  
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14 87 precise shape of the dose-relationship between HbA1c and high frequency hearing  
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17 88 impairment. Furthermore, no study has yet investigated whether HbA1c is associated  
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20 89 with hearing impairment among those with diabetes.  
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23 90 In Japan, a pure-tone audiometric test is mandatory in annual occupational health  
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26 91 check-ups (16). The large sample size this affords has enabled us to investigate the  
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29 92 dose-response relationship between HbA1c and hearing impairment, while accounting  
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32 93 for well-known risk factors of hearing impairment such as gender and smoking (17, 18).  
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34 94 The present study had two aims. The first aim was to investigate the association  
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37 95 between HbA1c and the incidence of hearing impairment using a large dataset from  
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40 96 annual occupational health check-ups in Japan, accounting for gender and smoking  
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43 97 status. The second aim was to determine whether HbA1c was associated with hearing  
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46 98 impairment among participants with diabetes.

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## 50 51 100 **METHODS**

### 52 53 54 101 Study population



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6 102 The present study was conducted using data from annual health check-ups of Japanese  
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9 103 workers. The All Japan Labor Welfare Foundation, a health service provider with  
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11 104 centers in Tokyo, Aomori, Nagano, Yamagata, Ibaraki, Gunma and Nagoya provided the  
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14 105 data from April 2008 through Dec 2015, allowing a maximum of 7 years of follow-up.  
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17 106 In Japan, annual health check-ups are mandatory for all employees and include a  
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20 107 hearing test under the Industrial Safety and Health Act. Nearly all employees attend a  
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23 108 health check-up every year. Participants were mainly Japanese employees but also  
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26 109 included a small number of their dependents, employers and foreign workers.  
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29 110 A total of 312,512 participants aged 30-65 years underwent a hearing test and HbA1c  
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31 111 test at baseline (between Apr 2008 and Mar 2009). Of these, we excluded participants  
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34 112 with hearing impairment at baseline (n=51,489). Given that diabetic patients with  
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37 113 complications may receive more intensive treatments, which may bias the association  
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40 114 between HbA1c and hearing impairment, we excluded participants with cardiovascular  
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43 115 disease and stroke (n=913). We further excluded participants who did not attend any  
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46 116 subsequent health examinations or hearing tests (n=48,618). After further exclusion of  
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49 117 8,517 participants with missing information on covariates (5,011 for smoking status,  
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51 118 5,152 for alcohol consumption, 1,815 for physical activity data, 5 for body mass index  
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54 119 (BMI), 9 for hypertension and 9 for dyslipidemia data; some participants had missing

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6 120 data for more than one parameter), leaving 202,975 participants (131,689 men and  
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9 121 71,286 women) for analysis.  
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11 122 Ethics  
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14 123 We obtained written informed consent from each participant who attended the health  
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17 124 check-up after April 2013. Before March 2013, we disclosed the purpose of our study  
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20 125 by posters and the participants had the opportunity to refuse the use of their data for the  
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23 126 study. This procedure conforms to the Japanese Ethical Guidelines for Medical and  
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26 127 Health Research Involving Human Subjects, where the obtaining consent may be  
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29 128 simplified for observational studies using existing data. The research protocol including  
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32 129 consent procedure was approved by the Ethics Committee of the Faculty of Medicine,  
33  
34 130 Toho University (No. 25017 and No.A16130) and the Ethics Committee of the National  
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37 131 Center for Global Health and Medicine (No. NCGM-G-001254-02).  
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40 132 Ascertainment of hearing impairment  
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43 133 Trained staff performed pure-tone air-conduction audiometry using an audiometer  
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46 134 (AA-57, RION Inc., Tokyo, Japan). Low frequency hearing impairment was defined as  
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49 135 failure to hear a pure-tone signal of 30dB at 1 kHz in the better ear, and high frequency  
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52 136 hearing impairment as failure to hear a pure-tone signal of 40dB at 4 kHz in the better  
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55 137 ear. These thresholds are recommended for use in annual health check-ups by Ministry  
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6 138 of Health, Labor and Welfare in Japan (16). Onset of hearing impairment was defined as  
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9 139 the day of the health check-up on which hearing impairment was first detected.  
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11 140 Data collection and measurements at baseline (between Apr 2008 and Mar 2009)  
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14 141 We used a self-administered questionnaire developed by the Ministry of Health, Labor  
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17 142 and Welfare for a specific health examination, namely the national health checkup  
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20 143 system focused on metabolic syndrome (19), to assess medical history, regular physical  
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23 144 activity (walking time  $<60$  min/day or  $\geq 60$  min/day), smoking status (non-smoker, daily  
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26 145 smoker  $\leq 20$  cigarettes/day or  $>20$  cigarettes/day), alcohol consumption (non-drinker,  $<1$   
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29 146 *go*, 1 to  $<2$  *go* or  $\geq 2$  *go*/day; one *go* of sake, a traditional Japanese beverage, is equal to  
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32 147 about 180 mL of 10-14% ethanol and contains about 23 g of ethanol) (20), and  
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35 148 self-reported diabetes (treatments with anti-diabetic medication or a self-reported  
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38 149 history of diabetes: yes or no). Job type was categorized as professional job,  
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41 150 management, office job, sales, service, telegraph, manufacturing, transportation and  
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44 151 other. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body  
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47 152 mass index (BMI) was calculated as the weight in kilograms divided by the square of  
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50 153 height in metres and categorized into 4 groups ( $<18.5$ , 18.5-22.9, 23-29.9,  $\geq 30$  kg/m<sup>2</sup>).  
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53 154 Blood pressure was measured in the sitting position using an automated  
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56 155 sphygmomanometer (HEM-907, Omron, Kyoto, Japan). Participants with high blood

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6 156 pressure ( $\geq 130$  mmHg systolic or  $\geq 85$  mmHg diastolic) received a second measurement  
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9 157 and the average was used for the analysis. Hypertension was defined by  $\geq 140$  mmHg  
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11 158 systolic,  $\geq 90$  mmHg diastolic or the use of medication for hypertension. A venous blood  
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14 159 sample was collected and stored in a cooler at 4 °C for transportation to an external  
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17 160 laboratory (SRL, Tokyo, Japan). Triglyceride level was measured using an enzymatic  
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20 161 colorimetric test and high-density lipoprotein cholesterol (HDL-C) was determined  
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23 162 using a direct method. Dyslipidemia was defined by triglyceride  $\geq 150$  mg/dL (1.7  
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26 163 mmol/L) in men and women, HDL-C  $< 40$  mg/dL (1.04 mmol/L) in men and  $< 50$  mg/dL  
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29 164 (1.3 mmol/L) in women or use of medication for dyslipidemia. HbA1c was measured by  
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31 165 latex agglutination turbidimetry and converted to the National Glycohemoglobin  
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34 166 Standardization Program equivalent value (%) using the formula below, according to the  
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37 167 Japan Diabetes Society statement (21) :  
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40 168  $\text{HbA1c (\%)} = 1.02 \times \text{HbA1c (Japan Diabetes Society) (\%)} + 0.25\%$   
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43 169 Diabetes was defined as  $\text{FPG} \geq 126$  mg/dL,  $\text{HbA1c} \geq 6.5\%$ , or self-reported diabetes.  
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46 170 Statistical analysis  
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49 171 Participants were divided into 7 groups according to their HbA1c level at baseline  
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51 172 [ $< 5.0\%$  (31 mmol/mol), 5.0-5.4% (31-36 mmol/mol), 5.5-5.9% (37-41 mmol/mol),  
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54 173 6.0-6.4% (42-46 mmol/mol), 6.5-6.9% (48-52 mmol/mol), 7.0-7.9% (53-63 mmol/mol),  
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6 174  $\geq 8.0\%$  (64 mmol/mol)]. The HbA1c group specific baseline characteristics of  
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9 175 participants were described as means (SD) for continuous variables and percentages for  
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11  
12 176 categorical variables. Person-years was calculated from baseline to the onset of hearing  
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15 177 impairment, or the date of the last health check-up through Dec 2015 (whichever  
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18 178 occurred first). Crude incident rates of hearing impairment were shown in events per  
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20  
21 179 1000 person-years. Survival analyses were performed using Cox regression to estimate  
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23  
24 180 the hazard ratio (HR) with 95% confidence interval (CI) for the incidence of hearing  
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27 181 impairment across HbA1c categories, with 5.0-5.4% (31-36mmol/mol) as the reference  
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29  
30 182 value. The analyses were stratified by sex because the interaction between hearing  
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33 183 impairments and sex was significant ( $p$  for interaction  $<0.001$ ). Age-adjusted model  
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36 184 (model 1) and multiple-adjusted model (model 2), which included alcohol consumption,  
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39 185 physical activity, BMI, hypertension, dyslipidemia, self-reported diabetes and smoking  
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42 186 status were used for the analysis. Although smoking status itself was related to hearing  
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45 187 impairment in this study, the association between HbA1c and hearing impairment  
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48 188 differed according to smoking status ( $p$  for interaction  $<0.001$ ). We therefore  
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50  
51 189 additionally performed analyses according to combined HbA1c (7 groups) and smoking  
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54 190 status (non-smoker and current smoker), by considering HbA1c 5.0-5.4%  
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57 191 (31-36mmol/mol) and non-smoker as the reference category. We did not analyze

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6 192 women's smokers because of the small number of cases. To assess whether control of  
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9 193 HbA1c would reduce the incidence of hearing impairment in those with diabetes, we  
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11 194 elucidated the shape of the relationship between HbA1c and high frequency hearing  
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14 195 impairment among those with diabetes. We fitted restricted cubic splines models with  
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17 196 seven knots placed at the 1th, 5th, 25th, 50th, 75th, 95th, and 99th centiles as reference  
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20 197 values of HbA1c 6.6% (25th) (22). The HRs were adjusted for alcohol consumption,  
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23 198 physical activity, BMI, hypertension, dyslipidemia and smoking status. As a sensitivity  
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26 199 analysis, we further adjusted for job type in the main analyses (model 2) among  
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29 200 participants with this information (n=126,823). We tested the proportional hazards  
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32 201 assumption using Schoenfeld residuals. We found no significant deviations for any  
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35 202 covariate. P value of two-tailed test <0.05 was considered statistically significant. Trend  
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38 203 association was assessed by assigning ordinal numbers (0–6) to the HbA1c categories.  
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41 204 We calculated the p for the quadratic trend because it was a better fit for the data than  
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44 205 the simple linear model. All statistical analyses were performed using Stata version 12.1  
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47 206 (StataCorp, College Station, Texas, USA).

#### 207 Patient and public involvement

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

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6 210 **RESULTS**

7  
8 211 Baseline characteristics by category of HbA1c are shown in Table 1. The mean age of  
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10 212 participants was 45 years for men and 47 years for women. Participants who had higher  
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12 213 HbA1c tended to be non-drinkers and to have higher BMI, hypertension, and  
13  
14 214 dyslipidemia in both men and women. Male participants with higher HbA1c tended to  
15  
16 215 be smokers consuming > 20 cigarettes per day.

17  
18 216 In men, 4,621 developed high frequency hearing impairment with 661,937 person-years  
19  
20 217 (mean duration of follow-up was 5.0 years) and 1,311 developed low frequency hearing  
21  
22 218 impairment with 670,153 person-years (5.1 years). In women, 582 developed high  
23  
24 219 frequency hearing impairment with 345,312 person-years (4.8 years) and 1,207  
25  
26 220 developed low frequency hearing impairment with 344,057 person-years (4.8 years).

27  
28 221 Table 2 shows the association between HbA1c and the incidence of hearing impairment.  
29  
30 222 In the multivariable-adjusted model, HbA1c showed a quadratic trend with the  
31  
32 223 incidence of high frequency hearing impairment in men (p for quadratic=0.007), and a  
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34 224 statistically marginal association in women (p for quadratic=0.08). HbA1c was not  
35  
36 225 associated with low frequency hearing impairment. Figure 1 shows the association  
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38 226 between HbA1c and high frequency hearing impairment with accounting for smoking  
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40 227 status [the interaction between HbA1c and smoking status (p for interaction <0.001)].  
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6 228 Compared to non-smokers with HbA1c 5.0-5.4% (31-36mmol/mol), non-smokers with  
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9 229 HbA1c  $\geq$ 8.0% (64 mmol/mol) showed an association with hearing impairment [HR  
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11 230 (95%CI) of 1.46 (1.11-1.92) in men and 2.36 (1.34-4.15) in women]. Although smokers  
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14 231 had higher HRs of hearing impairment than non-smokers, HbA1c level was not  
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17 232 associated with hearing impairment among smokers. Additional adjustments for job  
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20 233 type did not affect the results (Appendix 1).

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22  
23 234 Figure 2 shows the spline regression model of high frequency hearing impairment at  
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26 235 various HbA1c levels against a reference HbA1c level of 6.6% in participants with  
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29 236 diabetes at baseline (n=10,154). The relationship between HbA1c and the incidence of  
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32 237 hearing impairment was J-shaped, with the significant increase of HR for HbA1c $\geq$ 7.2%.

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## 35 36 37 239 **DISCUSSION**

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40 240 In this study, we found a quadratic trend between HbA1c and the incidence of  
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43 241 high frequency hearing impairment. In particular, HbA1c concentrations over 8.0% (64  
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46 242 mmol/mol) were associated with high frequency hearing impairment among  
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49 243 non-smokers. A J-shaped association between HbA1c and high frequency hearing  
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52 244 impairment was observed among participants with diabetes at baseline. Our findings



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6 245 indicate that appropriate glycemic control may prevent the incidence of diabetic hearing  
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9 246 impairment.

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11 247 Our finding of a quadratic trend between HbA1c and hearing impairment is  
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14 248 supported by the results of two longitudinal studies. (13, 15) One of these reported an  
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17 249 odds ratio (95% CI) of high frequency hearing impairment per 1.0% increase in HbA1c  
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20 250 of 1.52 (1.03 to 2.23), albeit no statistical association between the three categories of  
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23 251 HbA1c and high frequency hearing impairment (13). The second reported that HbA1c  
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26 252 was positively associated with average hearing threshold, mainly among low  
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29 253 frequencies (15). The present study provides novel evidence that an HbA1c of 8.0% (64  
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31 254 mmol/mol) or above is associated with increased risk of high frequency hearing  
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34 255 impairment in non-smokers. Our findings are consistent with the work of Cruickshanks  
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37 256 et al., who reported that poor glycemic control, defined by a glycosylated hemoglobin  
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40 257 level, was associated with hearing impairment (23).

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42 258 Additionally, we found that the J-shaped association between HbA1c and  
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45 259 hearing impairment remained even among participants with diabetes at baseline. This  
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48 260 result suggests that proper glycemic control may prevent diabetic-related hearing  
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51 261 impairment even in those with diabetes. Previous studies have also reported a J-shaped  
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54 262 association between HbA1c and diabetics complications, and noted that hypoglycemia

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6 263 might increase diabetic complications (24-26). More research is needed to determine a  
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9 264 suitable HbA1c level for glycaemic targeting to prevent hearing impairment in diabetic  
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12 265 management.

13  
14 266 We found that high frequency hearing impairment has a quadratic trend with  
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17 267 HbA1c among non-smokers but not smokers. Previous studies have reported an adverse  
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20 268 effect of smoking cigarettes on hearing impairment (23, 27, 28). It is plausible that the  
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23 269 effect of smoking cigarettes may be stronger than HbA1c and might mask the effect of  
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26 270 HbA1c. Further research is needed to confirm the joint effect of smoking and HbA1c on  
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29 271 hearing impairment.

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31 272 The pathophysiology underlying high-HbA1c-associated hearing impairment is  
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34 273 unclear, which allows for speculation. One possible explanation is that  
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37 274 hyperglycaemia-related microvascular complications lead to thickening of the cochlea  
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40 275 and vestibulopathy, and result in hearing impairment (7, 8, 29-33). Diabetic-related  
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43 276 hearing impairment has been mainly observed at high frequencies, suggesting that high  
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46 277 frequency-specific areas of the cochlea may be more fragile to ischemic changes due to  
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49 278 microvascular complications (34-38). This mechanism is supported by the J-shaped  
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51 279 association between HbA1c and hearing impairment observed in the present study, since  
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6 280 previous studies also reported a J-shaped-association between HbA1c and diabetic

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9 281 vascular complications (39, 40). Further studies to confirm this idea are required.

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11 282 This study has several strengths. The large dataset allowed us to investigate the

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14 283 association between HbA1c and hearing impairment with comprehensive adjustment for

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17 284 covariates, and additionally, among participants with diabetes at baseline. Audiometry

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20 285 to confirm hearing impairment was conducted by trained staff. Several limitations of the

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23 286 study also need to be considered. First, though noise exposure is an important risk factor

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26 287 on hearing impairment (41, 42), information on noise exposure was not available and

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29 288 thus noise information was not considered in the analyses. The present study thus might

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32 289 include the confounding influence of noise exposure. However, a previous study reported

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35 290 that the relationship between diabetes and hearing impairment was independent of this

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38 291 variable (37). Moreover, in the present study, HbA1c level was associated with hearing

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41 292 impairment even after accounting for job type in a sensitivity analysis. Second,

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44 293 information on ototoxic drug use, ear surgery, and ear infection was not collected, and

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47 294 we were therefore unable to exclude cases of hearing impairment due to these factors.

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50 295 Third, blood pressure was measured once, followed by a second measurement if the first

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53 296 systolic blood pressure  $\geq 130$  mmHg systolic or diastolic blood pressure  $\geq 85$  mmHg. All

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56 297 participants didn't have the same evaluation of blood pressure. This may lead to

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6 298 misclassification of hypertension. Fourth, we did not account for gender or smoking  
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8 299 status in the association between HbA1c and hearing impairment for participants with  
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11 300 diabetes because of the small sample size. Fifth, the hearing test was only conducted at  
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14 301 1 kHz and 4 kHz. Hearing impairment at other frequencies could not therefore be  
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17 302 identified. Sixth, we cannot exclude the possibility of residual confounding and  
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20 303 confounding by unmeasured variables. Finally, the study participants were mainly  
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23 304 workers, and thus caution is required when generalizing our findings.  
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## 25 305 **CONCLUSION**

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28 306 We found the quadratic trend between HbA1c and the incidence of high  
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31 307 frequency hearing impairment in non-smokers. The trend between HbA1c and hearing  
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34 308 impairment remained even among those with diabetes. These findings indicate that  
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37 309 diabetic-related hearing impairment may be prevented with appropriate glycemetic  
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40 310 control. These findings warrant confirmation in interventional studies.  
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## 42 311 Abbreviations

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45 312 HbA1c: hemoglobin A1c; BMI: body mass index; HR: hazard ratio; CI: confidence  
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48 313 interval  
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## 50 314 Acknowledgements

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6 315 The authors would like to thank Dr Nobuo Yanagisawa and Dr Takeshi Kawaguchi for  
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8  
9 316 coordinating the study.

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11 317 Contributors

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13  
14 318 SN, TaM and IK designed study and drafted the manuscript. SN, HHH, KaK, AN and  
15  
16  
17 319 KeK performed the data analysis. MD collected and interpreted the data. All authors  
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20 320 participated in interpretation of the findings, revised the paper critically for important  
21  
22  
23 321 intellectual content and approved the final version to be published. YN and YM  
24  
25  
26 322 provided administrative, technical and material support. TM and SA revised the work  
27  
28  
29 323 critically for important intellectual content. SN and YN are guarantors.

30  
31 324 Funding

32  
33  
34 325 This research was funded by All Japan Labor Welfare Foundation Research Fellowship.

35  
36  
37 326 Competing interests

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40 327 SN is occupational physicians in All Japan Labor Welfare Foundation. All Japan Labor  
41  
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43 328 Welfare Foundation had no role in the design, analysis or writing of this articles. All  
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46 329 other authors declare no competing financial interests.

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48 330 Ethics approval

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6 331 The research protocol was approved by the Ethics Committee of the Faculty of  
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8 332 Medicine, Toho University and the Ethics Committee of the National Center for Global  
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11 333 Health and Medicine.  
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14 334 Data sharing statement  
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17 335 No additional data are available.  
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For peer review only

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Table 1 Baseline characteristics of study participants according to HbA<sub>1c</sub> (n=202,975).

	HbA <sub>1c</sub> (%) (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)
<b>Men</b>								
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 <sup>†</sup>	35	32	35	36	34	34	30	32
Drinker 1 to <2 go/day <sup>†</sup>	26	30	27	25	25	25	26	22
Drinker ≥2 go/day <sup>†</sup>	12	19	13	10	10	11	11	10
Self-reported diabetes (%) <sup>‡</sup>	2.3	0.07	0.10	0.4	4.6	22.4	41.1	37.3
BMI (kg/m <sup>2</sup> )*	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 (%) <sup>§</sup>	28	21	22	29	44	57	57	53
Dyslipidemia (%) <sup>  </sup>	39	29	33	41	54	59	60	65
<b>Women</b>								
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 <sup>†</sup>	31	36	34	29	26	22	22	19
Drinker 1 to <2 go/day <sup>†</sup>	6.8	14.4	7.8	5.0	3.8	3.9	3.7	2.7
Drinker ≥2 go/day <sup>†</sup>	1.7	5.3	1.9	1.0	0.5	0.6	0.5	0.7
Self-reported diabetes (%) <sup>‡</sup>	1.2	0.05	0.03	0.1	2.5	17.4	38.2	47.5
BMI (kg/m <sup>2</sup> )*	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 (%) <sup>§</sup>	19	11	14	21	34	52	59	53
Dyslipidemia (%) <sup>  </sup>	22	13	16	24	39	54	61	59

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

\* Mean (SD)

<sup>†</sup> One go contains ~23g of ethanol.

<sup>‡</sup> Self-reported diagnosis of diabetes or receiving medication.

<sup>§</sup> Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90 mmHg or receiving medication.

<sup>||</sup> 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 mmol/L) in women or receiving medication.

Table 2 Hazard ratio of hearing impairment according to baseline HbA<sub>1c</sub> (n = 202,975).

		HbA <sub>1c</sub> (%) (mmol/mol)							P for quadratic
		<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)	
<b>Low frequency</b>									
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
<b>High frequency</b>									
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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5 454 **Fig1.** The association between HbA1c and hearing impairment of high frequency stratified by smoking status.  
6 455 Footnote; Results obtained by multivariable Cox regression. The reference value was 5.0-5.4% of HbA1c in  
7 456 non-smoker. The model was adjusted for age (year, continuous), sex, body mass index (<18.5, 18.5-22.9, 23-29.9, or  
8 457  $\geq 30.0$  kg/m<sup>2</sup>), alcohol consumption (non-drinker, drinker consuming <1, 1 to <2, or  $\geq 2$  go of Japanese sake  
9 458 contains approximately 23g of ethanol), walking time (<60, or  $\geq 60$  min/day), self-reported diabetes, hypertension  
10 459 (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and  
11 460 hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level <40 mg/dL or receiving  
12 461 medication).

For peer review only



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5 **Fig 2.** Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline  
6 (n=10,154).  
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8 Footnote; Results obtained by multivariable Cox regression with restricted cubic splines with seven knots (p1, p5,  
9 p25, p50, p75, p95 and p99). The reference value was 6.6% (p25) of HbA1c. The continuous line presents hazard  
10 ratios and the dashed line presents 95% confidence intervals. The model was adjusted for age (year, continuous), sex,  
11 body mass index (<18.5, 18.5-22.9, 23-29.9, or  $\geq 30.0$  kg/m<sup>2</sup>), smoking status (non-smoker, smoker consuming  $\leq 20$ ,  
12 or  $> 20$  cigarettes per day), alcohol consumption (non-drinker, drinker consuming  $<1$ ,  $1$  to  $< 2$ , or  $\geq 2$  go of Japanese  
13 sake contains approximately 23g of ethanol), walking time (  $<60$ , or  $\geq 60$  min/day), hypertension (systolic blood  
14 pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride  
15 level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level  $<40$  mg/dL in men and  $<50$  mg/dL in women or  
16 receiving medication).  
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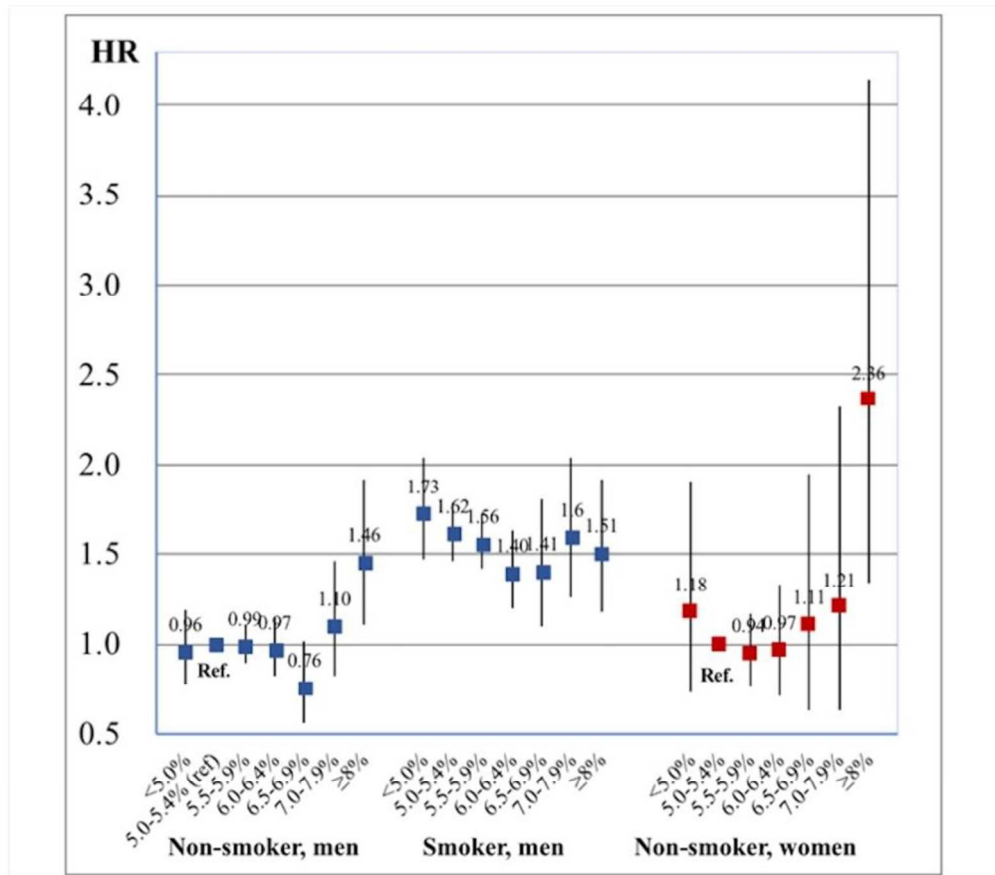


Fig1. The association between HbA1c and hearing impairment of high frequency stratified by smoking status.

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/m<sup>2</sup>), 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).

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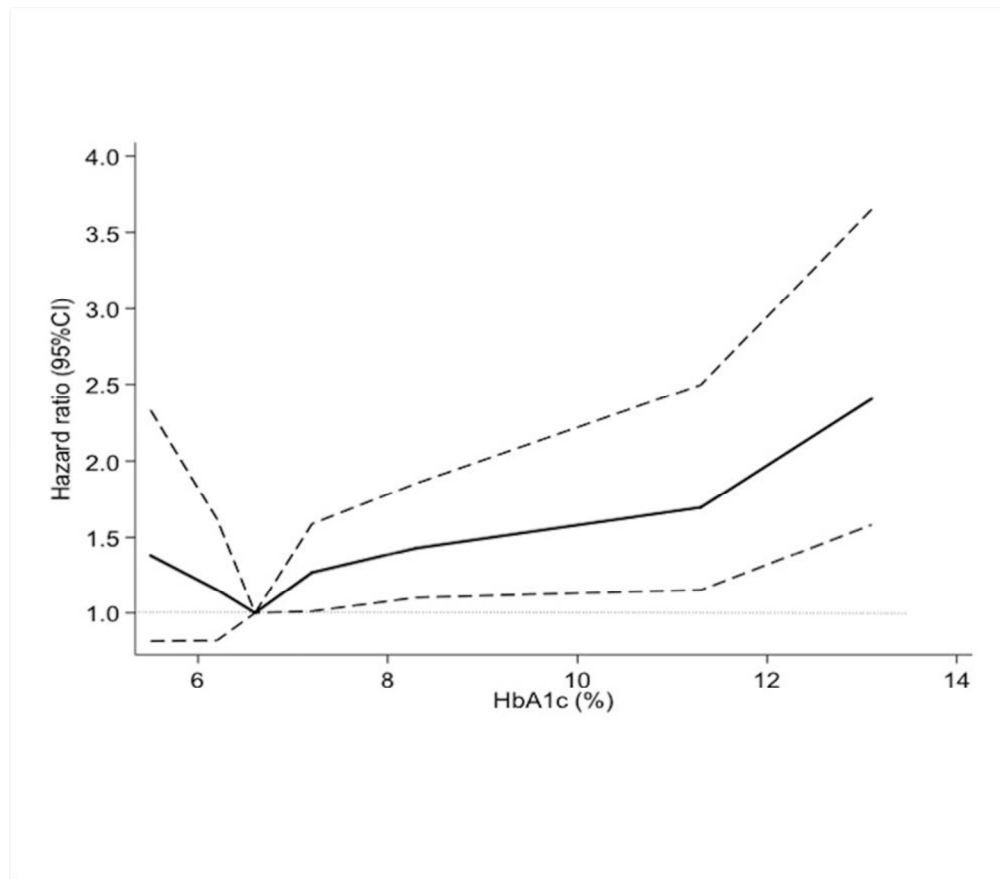


Fig 2. Adjusted hazard ratio of high frequency hearing impairment among participants with diabetes at baseline (n=10,154).

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  $\geq 30.0$  kg/m<sup>2</sup>), smoking status (non-smoker, smoker consuming  $\leq 20$ , or  $> 20$  cigarettes per day), alcohol consumption (non-drinker, drinker consuming  $<1$ , 1 to  $< 2$ , or  $\geq 2$  go of Japanese sake contains approximately 23g of ethanol), walking time (  $<60$ , or  $\geq 60$  min/day), hypertension (systolic blood pressure  $\geq 140$ mmHg, diastolic blood pressure  $\geq 90$  mmHg or receiving medication), and hyperlipidemia (triglyceride level  $\geq 150$ mg/dL, high-density lipoprotein cholesterol level  $<40$  mg/dL in men and  $<50$  mg/dL in women or receiving medication).

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Appendix 1. The association between baseline HbA<sub>1c</sub> and Incidence of high frequency hearing impairment (n=126,823).

		HbA <sub>1c</sub> (%) (mmol/mol)							P for quadratic
		<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)	
<b>Men</b>	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
<b>Women</b>	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.

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

	Item No	Recommendation	Page number
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P1 Line1 P3 Line31, P4 Line51
<b>Introduction</b>			
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
<b>Methods</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	P7 Line99-108
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 (b) Describe any methods used to examine subgroups and interactions	P10 Line157-193 P11 Line173-

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(c) Explain how missing data were addressed

P7

Line105-

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(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

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(e) Describe any sensitivity analyses

P12

Line185-

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<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	P12 Line201-206
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	P12 Line200-206
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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-

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**Other information**


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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
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\*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](http://www.strobe-statement.org).