

Systolic Blood Pressure and Objective Hearing Thresholds Among Japanese Middle-Aged Adults: A Facility-Based Retrospective Cohort Study

Short running head: Systolic Blood Pressure and Hearing Thresholds

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The authors declare that they have no conflicts of interest with respect to this research study and paper.

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1 **ABSTRACT**

2 **Introduction:** Very few studies have compared the magnitude of the changes in the hearing thresholds at 1
3 kHz and 4 kHz according to the systolic blood pressure (SBP). We investigated the effects of SBP on repeated
4 measures of hearing threshold using pure-tone audiometry.

5 **Methods:** This retrospective cohort study included 5,479 (for the analysis at 1 kHz) and 2,045 (for 4 kHz)
6 individuals aged 50–59 years who underwent facility-based health checkups. A multivariable generalized
7 linear mixed model was constructed for the analysis at 1 kHz and 4 kHz.

8 **Results:** The mean follow-up durations were 30,262 and 7,454 person-years, respectively. The interaction of
9 SBP and year was significantly associated with the change in hearing threshold in both analyses at 1 kHz
10 (with estimated slope, 0.00080; 95% confidence interval [CI], 0.00049–0.00110) and 4 kHz (with estimated
11 slope, 0.0042; 95% CI, 0.0028–0.0057). The 10-year changes in hearing threshold with baseline SBP of 110
12 and 140 mmHg were 0.4 and 0.6 dB at 1 kHz and 1.0 and 2.3 dB at 4 kHz, respectively.

13 **Conclusions:** Higher SBP was associated with an increased hearing threshold at both 1 and 4 kHz among
14 middle-aged individuals.

15
16 **Keywords:** Epidemiology; Hearing loss; Hypertension; Japanese population; Longitudinal study; Middle-
17 aged

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INTRODUCTION

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In 2019, the Global Burden of Disease Study showed that 1.6 billion individuals experienced hearing impairment (HI) (1), and a global economic cost exceeding 981 billion USD (2). Furthermore, the disability-adjusted life-years (DALYs) for HI was the ninth and tenth top cause of DALY counts for individuals aged 50–74 years and ≥ 75 years, respectively (3).

Hypertension-related hearing impairment (HI) has the same audiometric characteristics as age-related HI (4), which is more pronounced at higher frequencies with a gradual and symmetric progression (4,5). The previous study, which utilized measured systolic blood pressure (SBP) and audiometry evaluation results, reported that higher SBP was associated with HI at 1 kHz among individuals aged 20–59 years who received health checkups at a facility in Japan (6). However, that study did not focus on the change in hearing threshold and could not estimate the effect of higher SBP on HI because the analytic model was constructed to examine the hazard ratios of HI (6). Additionally, that study treated young- and old-onset HI together (6), despite the difference in etiology. Moreover, no clear association was observed at 4 kHz as of yet (6).

In this study, we hypothesized that higher SBP levels were associated with a higher hearing threshold and HI was more pronounced at higher frequency among middle-aged adults, who had higher prevalence of HI. Therefore, we investigated the association between SBP and measured hearing thresholds by pure-tone audiometry at 1 kHz and 4 kHz in individuals aged 50–59 years using facility-based health checkup data.

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MATERIALS AND METHODS

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Study Design and Participants

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This facility-based retrospective cohort study was conducted using data from medical records at the health checkup department of [Author's institution]. The participants were aged 50–59 years and underwent audiometry evaluation two times or more during health checkups at [Author's institution] between April 2007 and March 2020. For the analysis at 1 kHz and 4 kHz, 5,479 and 2,045 individuals, respectively, without HI at baseline were included. The details are shown in the Supplemental Digital Content.

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The study protocol and use of existing data were approved by the ethics committee of [Author's institution] (Approval Number: @@@). It was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The participants were allowed to drop out of the study via the hospital's website.

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Variables

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We collected information about SBP, the left and right hearing thresholds, age, sex, and the variables based on the risk factors of HI reported before (5). No information regarding ear diseases or noise exposure was available. The precise method can be found in the Supplemental Digital Content.

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There were missing values for serum glucose levels, serum low-density lipoprotein cholesterol levels, current smoking and drinking status, regular exercise, and antihypertensive medication use. The percentage of missing values across the six variables varied between 34.0 to 35.3% (out of 5,479 records),

57 and 9.5 to 11.4% (out of 2,045 records) in the analysis at 1 and 4 kHz, respectively. A total of 1,992 (36.4%)
58 and 247 (12.1%) records were incomplete, respectively. A compact display of patterns of missingness with
59 covariates is presented in Tables S1 and S2 in Supplemental Digital Content for the analysis at 1 kHz and 4
60 kHz, respectively.

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Statistical Analysis

63 The baseline characteristics of the participants according to their SBP were presented as the mean
64 values of continuous variables and proportions of categorical variables. A multivariable generalized linear
65 mixed model was constructed to evaluate the effects of SBP on repeated measures of hearing threshold with
66 first-order autoregressive modeling. The missing values of the covariates at baseline were processed using
67 multiple imputation methods. The precise method for statistical analysis is shown in the Supplemental Digital
68 Content.

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RESULTS

The baseline characteristics of the study population according to the tertile levels of SBP are shown in Table 1. Among the participants for the analysis at 1 kHz and 4 kHz, there were 2,807 (51.2%) and 866 (42.3%) men, and the mean age was 52.7 (3.0 standard deviation [SD]) and 51.8 (2.6 SD) years, respectively. The SBP was positively correlated with age, sex (male), body mass index, antihypertensive medications, diabetes, hyperlipidemia, alcohol intake, and exercise habits.

The effects of the variables in the generalized linear mixed model are presented in Table 2. The mean follow-up durations were 30,262 and 7,454 person-years at 1 kHz and 4 kHz, respectively. In both analyses, the interaction between SBP levels and year was significantly associated with the change in hearing threshold. The parameter estimate of the interaction at 4 kHz was higher than that at 1 kHz. Compared with the results under fully conditional specification (FCS) to impute missing variables, the results under Markov chain Monte Carlo (MCMC) were consistent (Table S3 in Supplemental Digital Content).

According to the multivariable model, the slope of the hearing threshold of participants with an SBP of 140 mmHg was higher than participants with an SBP of 110 mmHg, for both the 1 kHz and 4 kHz analyses (Fig. 1). The 10-year changes in hearing threshold among participants with baseline SBP of 110 and 140 mmHg were 0.4 and 0.6 dB at 1 kHz ($p < 0.001$) and 1.0 and 2.3 dB at 4 kHz ($p < 0.001$), respectively.

DISCUSSION

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90 This retrospective cohort study focused on the change value of hearing thresholds among middle-
91 aged participants from a single health facility, comparing the magnitudes between the changes in hearing
92 thresholds at 1 kHz and 4 kHz according to SBP levels. In this study, a higher SBP level was associated with
93 an increased hearing threshold at both 1 kHz and 4 kHz for middle-aged people. There was a higher
94 difference between the model-predicted change in the hearing threshold at 4 kHz than at 1 kHz according to
95 SBP levels. Our results suggested that hypertension-related HI was more pronounced at 4 kHz than 1 kHz,
96 which was in line with the prior findings (4).

97 To the best of our knowledge, twelve longitudinal studies on this topic have been conducted (6-

98 17); however, only four studies utilized pure-tone hearing threshold as the continuous variable (7-10).

99 Moreover, there were two longitudinal studies that utilized speech-in-noise performance (7,11). The

100 Atherosclerosis Risk in Communities (ARIC) Study, a population-based cohort study in the USA, published

101 two investigations (7,8). The first report revealed a positive association between the slope of pure-tone

102 average levels at four frequencies (0.5, 1, 2, and 4 kHz) in the better-hearing ear and an increment of SBP

103 among individuals aged 41–65 years (8). This result corroborates our result. The other report of the ARIC

104 Study with individuals aged 44–65 years revealed that hypertension at either midlife or late life, and its

105 change was not associated with hearing threshold measured by pure-tone audiometry based on the average

106 levels at four frequencies (0.5, 1, 2, and 4 kHz) in the better-hearing ear (7). Meanwhile, individuals with

107 hypertension at both midlife and late life had a higher risk of low speech-in-noise performance (7). That

108 study investigated the association between midlife to late life change patterns in blood pressure and HI
109 measured by pure-tone audiometry; however, no obvious difference was observed. A Brazilian cohort study
110 yielded consistent results with ours (9). A web-based Dutch study revealed that hypertension was associated
111 with a higher speech reception threshold among individuals aged 18–70 years (11). Another Dutch cohort
112 study assessing showed no association between measured hypertension and HI (10). We did not fully
113 investigate the association between blood pressure trajectory and development of HI. We also did not look
114 into the effect of antihypertensive treatments on the prevention of HI; hence, further investigations are
115 warranted.

116 Understanding the potential underlying mechanisms of hypertension in the development of HI is
117 important. Hypertension may reduce the capillary blood flow to the cochlea and auditory nerve (4). Higher
118 natriuretic peptide levels associated with hypertension may also inhibit the potassium pump within the stria
119 vascularis of the cochlea, which disrupt ionic homeostasis in the inner ear fluids and depolarization of hair
120 cells (4). Although these mechanisms are not yet fully elucidated, these processes could lead to cochlear
121 damage and eventual sensorineural HI (4).

122 This study had some limitations. First, the blood pressure and hearing threshold measurement
123 protocols were not standardized because the tests were performed during routine clinical practice, which is
124 not designed for research. Second, the one-time blood pressure measurement at checkup may not be
125 representative of the true blood pressure and we cannot rule out the possibility that this value may have been
126 accidentally high or low. Third, since the lower limit of the hearing threshold was 30 dB, the floor effect

127 should be considered. The difference in the true estimated slope may be smaller, especially if more floor
128 effect occurred among participants with low SBP at baseline. Fourth, we could not obtain information on
129 subjective hearing symptoms, which are important for assessing clinical significance. Fifth, determination
130 of the underlying hypertension mechanisms is not possible since we did not assess the types of HI (e.g.,
131 conductive, sensorineural, or mixed) due to the lack of detailed history, including the onset of HI. Sixth,
132 unmeasured factors, especially possible confounders (e.g., ear diseases and noise exposure), might have
133 biased the estimated effects (4,5,18). Seventh, the information on adjusted variables was incomplete
134 especially for the analysis at 1 kHz, which could have decreased the precision for the multiple imputation
135 analysis. Although the two methods of multiple imputation revealed similar results, our findings should be
136 interpreted with caution. Eighth, this study was conducted using data from a single facility, leading to
137 inadequate external validity. Thus, further studies, particularly multicenter or population-based prospective
138 studies are warranted.

139 In conclusion, higher SBP levels were associated with a higher hearing threshold at both 1 kHz
140 and 4 kHz among middle-aged individuals. HI due to higher SBP was more pronounced at 4 kHz than 1 kHz.
141 Further studies with repeated blood pressure and hearing threshold measurements are necessary to confirm
142 the effects of blood pressure trajectory and hypertension treatment for HI.

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REFERENCES

- 146 1. GBD 2019 Hearing Loss Collaborators. Hearing loss prevalence and years lived with disability, 1990-
147 2019: findings from the Global Burden of Disease Study 2019. *Lancet* 2021;397:996–1009.
- 148 2. McDaid D, Park AL, Chadha S. Estimating the global costs of hearing loss. *Int J Audiol* 2021;60:162–
149 70.
- 150 3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204
151 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.
152 *Lancet* 2020;396:1204–22.
- 153 4. Przewoźny T, Gójska-Grymajło A, Kwarciany M, Gąsecki D, Narkiewicz K. Hypertension and cochlear
154 hearing loss. *Blood Press* 2015;24:199–205.
- 155 5. Walling AD, Dickson GM. Hearing loss in older adults. *Am Fam Physician* 2012;85:1150–6.
- 156 6. Miyata J, Umesawa M, Yoshioka T, Iso H. Association between high systolic blood pressure and
157 objective hearing impairment among Japanese adults: a facility-based retrospective cohort study.
158 *Hypertens Res* 2022;45:155–61.
- 159 7. Ting J, Jiang K, Du S, et al. Longitudinal Blood Pressure Patterns From Mid- to Late Life and Late-Life
160 Hearing Loss in the Atherosclerosis Risk in Communities Study. *J Gerontol A Biol Sci Med Sci*
161 2022;77:640–6.
- 162 8. Reed NS, Huddle MG, Betz J, et al. Association of midlife hypertension with late-life hearing loss.
163 *Otolaryngol Head Neck Surg* 2019;161:996–1003.

- 164 9. Rolim LP, Samelli AG, Moreira RR, et al. Effects of diabetes mellitus and systemic arterial hypertension
165 on elderly patients' hearing. *Braz J Otorhinolaryngol* 2018;84:754–63.
- 166 10. Linssen AM, van Boxtel MP, Joore MA, Anteunis LJ. Predictors of hearing acuity: cross-sectional and
167 longitudinal analysis. *J Gerontol A Biol Sci Med Sci* 2014;69:759–65.
- 168 11. Goderie T, van Wier MF, Stam M, et al. Association between Speech Recognition in Noise and Risk
169 Factors of Cardiovascular Disease. *Audiol Neurootol* 2021;26:368–77.
- 170 12. Brant LJ, Gordon-Salant S, Pearson JD, et al. Risk factors related to age-associated hearing loss in the
171 speech frequencies. *J Am Acad Audiol* 1996;7:152–60.
- 172 13. Lasisi AO, Abiona T, Gureje O. The prevalence and correlates of self-reported hearing impairment in
173 the Ibadan study of ageing. *Trans R Soc Trop Med Hyg* 2010;104:518–23.
- 174 14. Shargorodsky J, Curhan SG, Eavey R, Curhan GC. A prospective study of cardiovascular risk factors
175 and incident hearing loss in men. *Laryngoscope* 2010;120:1887–91.
- 176 15. Lin BM, Curhan SG, Wang M, Eavey R, Stankovic KM, Curhan GC. Hypertension, diuretic use, and
177 risk of hearing loss. *Am J Med* 2016;129:416–22.
- 178 16. Olusanya BO, Davis AC, Hoffman HJ. Hearing loss grades and the International classification of
179 functioning, disability and health. *Bull World Health Organ* 2019;97:725–8.
- 180 17. Wu KL, Shih CP, Chan JS, et al. Investigation of the relationship between sensorineural hearing loss and
181 associated comorbidities in patients with chronic kidney disease: A nationwide, population-based cohort
182 study. *PLoS One* 2020;15:e0238913.

- 183 18. Basner M, Babisch W, Davis A, et al. Auditory and non-auditory effects of noise on health. *Lancet*
- 184 2014;383:1325–32.

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Figure Legends

186

FIG. 1 Multivariable model-predicted 5- and 10-year change in hearing thresholds at 1 kHz and 4 kHz

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according to the baseline systolic blood pressure (SBP) level. Figures in table represents estimates and

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standard deviations of hearing threshold in case of aged 50–54 years, body mass index of 21.0–22.9 kg/m²,

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and without antihypertensive medications, diabetes mellitus, hyperlipidemia, current smoking habits, alcohol

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intake, and exercise habits. Error bars represent 95% confidence intervals for estimates.

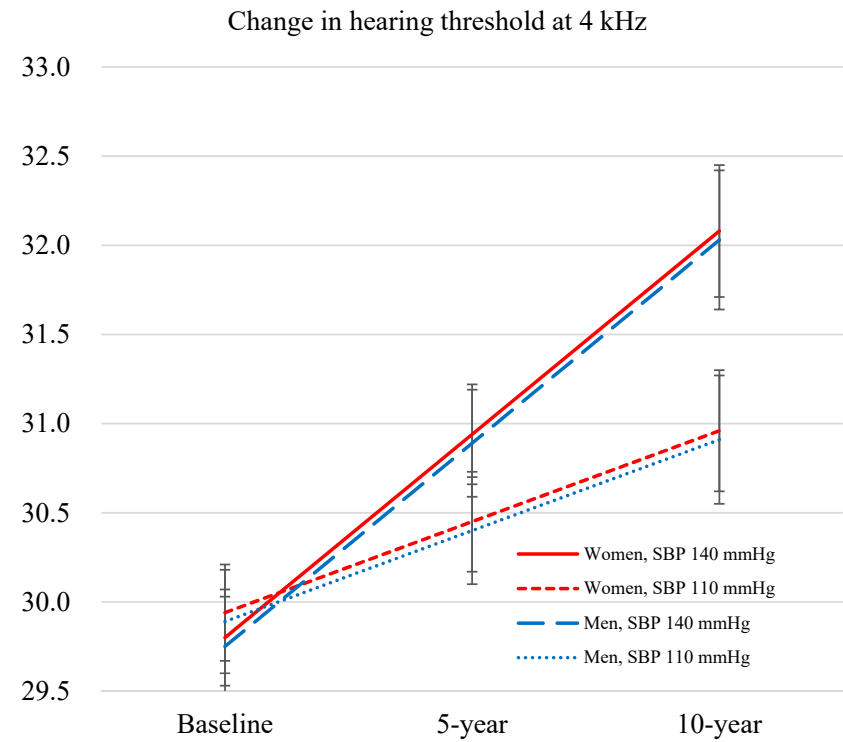
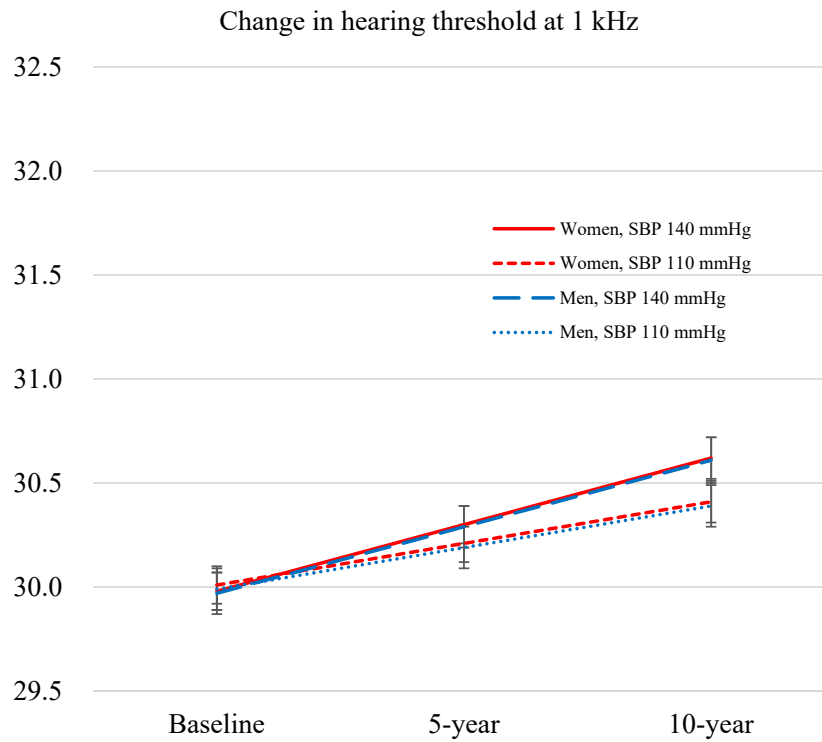
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List of Supplemental Digital Content

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SBP_and_HI_SDC_blinded_20221227.docx



Model	Analysis at 1 kHz			Analysis at 4 kHz		
	Baseline	5-year	10-year	Baseline	5-year	10-year
Women, SBP 140 mmHg	29.98 (0.05)	30.30 (0.05)	30.62 (0.05)	29.80 (0.14)	30.94 (0.14)	32.08 (0.19)
Women, SBP 110 mmHg	30.01 (0.05)	30.21 (0.05)	30.41 (0.05)	29.94 (0.14)	30.45 (0.14)	30.96 (0.17)
Men, SBP 140 mmHg	29.97 (0.05)	30.29 (0.05)	30.61 (0.05)	29.75 (0.14)	30.89 (0.15)	32.03 (0.20)
Men, SBP 110 mmHg	29.99 (0.05)	30.19 (0.05)	30.39 (0.05)	29.89 (0.15)	30.40 (0.15)	30.91 (0.18)

TABLE 1. Baseline characteristics according to the tertile systolic blood pressure levels

Characteristics	Participants in the analysis at 1 kHz (N=5,479)				Participants in the analysis at 4 kHz (N=2,045)			
	Systolic blood pressure (mmHg)				Systolic blood pressure (mmHg)			
	Tertile 1; 79–116 (N=1,879)	Tertile 2; 117–128 (N=1,727)	Tertile 3; 129–208 (N=1,873)	<i>p</i> for trend	Tertile 1; 81–115 (N=684)	Tertile 2; 116–128 (N=663)	Tertile 3; 129–208 (N=698)	<i>p</i> for trend
Age (year)	52.4 (2.9)	52.7 (3.0)	53.1 (3.1)	<.001	51.4 (2.4)	51.7 (2.7)	52.1 (2.8)	<.001
Men (%)	39.9	51.2	62.6	<.001	29.2	42.7	54.9	<.001
Body mass index (kg/m ²)	22.1 (3.0)	23.3 (3.3)	24.5 (3.6)	<.001	21.8 (3.1)	23.2 (3.4)	25.0 (4.0)	<.001
Antihypertensive medications (%)	6.7	15.7	26.5	<.001	5.6	15.2	24.9	<.001
Diabetes ^a (%)	4.4	6.7	11.8	<.001	3.6	6.5	11.8	<.001
Hyperlipidemia ^b (%)	38.7	46.9	45.3	<.001	31.7	38.6	42.1	<.001
Current smoking habits (%)	24.7	27.0	25.8	0.35	20.9	22.2	21.9	0.45
Alcohol intake								
No (%)	52.6	41.8	36.9	<.001	56.2	47.0	41.4	<.001
Occasional (%)	23.0	26.2	24.8	0.40	24.1	28.5	27.4	0.19
Everyday (%)	24.5	32.0	38.3	<.001	19.7	24.5	31.2	<.001
Exercise habits ^c (%)	13.1	17.4	18.3	0.01	14.0	16.7	18.8	0.05

Figures represent mean (standard deviation) or proportion

^a Serum glucose level ≥ 126 mg/dL or the use of antidiabetic medications

^b Serum low-density lipoprotein cholesterol level ≥ 140 mg/dL or the use of antihyperlipidemic medications

^c Once or more per week

TABLE 2. *Effects of variables in the generalized linear mixed model on hearing threshold at 1 kHz and 4 kHz*

Frequency	Analysis at 1 kHz (N=5,479)			Analysis at 4 kHz (N=2,045)		
	Parameter estimates (95% CI)	Standard error	p-value	Parameter estimates (95% CI)	Standard error	p-value
Age- and sex-adjusted model						
Intercept	30.0 (29.9 to 30.2)	0.1	<.001	30.6 (30.0 to 31.2)	0.3	<.001
SBP (mmHg)	-0.0005 (-0.0020 to 0.0010)	0.0007	0.50	-0.0039 (-0.0084 to 0.0007)	0.0023	0.09
Year	-0.046 (-0.084 to -0.008)	0.019	0.02	-0.39 (-0.57 to -0.21)	0.09	<.001
SBP (mmHg) * Year	0.00078 (0.00047 to 0.00108)	0.00016	<.001	0.0045 (0.0030 to 0.0059)	0.0007	<.001
Multivariable model ^{a,b}						
Intercept	30.1 (29.9 to 30.3)	0.1	<.001	30.4 (29.8 to 31.0)	0.3	<.001
SBP (mmHg)	-0.0009 (-0.0024 to 0.0007)	0.0008	0.28	-0.0045 (-0.0093 to 0.0003)	0.0024	0.06
Year	-0.047 (-0.085 to -0.009)	0.019	0.02	-0.37 (-0.55 to -0.19)	0.09	<.001
SBP (mmHg) * Year	0.00080 (0.00049 to 0.00110)	0.00016	<.001	0.0042 (0.0028 to 0.0057)	0.0007	<.001

CI, confidence interval; SBP, systolic blood pressure

^a Adjusted for age, sex, body mass index, antihypertensive medications, diabetes mellitus, hyperlipidemia, current smoking habits, alcohol intake, and exercise habits

^b Average number of all imputed datasets under fully conditional specifications

Supplemental Digital Content

Article Title

Systolic Blood Pressure and Objective Hearing Thresholds Among Japanese Middle-Aged Adults: A Facility-Based Retrospective Cohort Study

Journal Name

Otology & Neurotology

Authors

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Corresponding Author

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METHODS

Study Design

This facility-based retrospective cohort study was conducted using data from medical records at the health checkup department of [Author's institution]. This facility performs health screening for noncommunicable diseases among contractual company workers (86%), staff from [Author's institution] and affiliated nursing facilities (11%), and private individuals (3%) based on Japanese law and individual preference. Health screenings for hearing impairment (HI) is common in Japan even for individuals without a history of noise exposure.

The study protocol and use of existing data were approved by the ethics committee of [Author's institution] (Approval Number: 2019-5-2). It was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The participants were allowed to drop out of the study via the hospital's website.

Participants

The participants were aged 50–59 years and underwent audiometry evaluation two times or more during health checkups at [Author's institution] between April 2007 and March 2020. Baseline was defined as the first examination for each participant. A total of 5,895 individuals were included in the target age group. For the analysis, 5,479 and 2,045 individuals were finally included after excluding individuals with a hearing threshold of >30 dB at 1 kHz ($N=416$) and 4 kHz ($N=3,850$) at the baseline, respectively.

Variables

We collected information about age, sex, medications for hypertension, diabetes, and hyperlipidemia, current smoking habits, alcohol intake frequency, and exercise habits once or more times per week using the baseline questionnaire standardized according to the Japanese Ministry of Health, Labour and Welfare. No information regarding ear diseases or noise exposure was available. The body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared (kg/m^2) at baseline. The participants were classified into two groups according to age (50–54 and 55–59 years) and seven groups according to BMI (<18.5, 18.5–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, and ≥ 30.0 kg/m^2).

The primary blood pressure measurements were performed with automatic sphygmomanometers

31 (TM-2655P; A&D Company Ltd., Toshima, Tokyo, Japan before January 27, 2016, and Kentaro HBP-9020;
32 Omron Healthcare Co., Ltd., Muko, Kyoto, Japan after January 28, 2016) placed on the arm of the participants
33 while in a sitting position. If the blood pressure level was high (systolic blood pressure [SBP] ≥ 129 mm Hg or
34 diastolic blood pressure ≥ 85 mm Hg) or unreliable, the measurement was repeated or manual equipment was
35 used, and the reading with the lowest SBP level was selected.

36 The hearing test was performed by well-trained nurses using pure-tone audiometry with circumaural
37 headphones (AA-56; Rion Co., Ltd., Kokubunji, Tokyo, Japan before June 30, 2009, and AA-57; Rion Co., Ltd.
38 after July 1, 2009) in a quiet isolated room. The hearing thresholds of the participants were evaluated at 5 dB
39 intervals between 30 and 80 dB at 1 and 4 kHz, respectively. We used the average value of the left and right
40 hearing thresholds. Blood pressure and hearing thresholds were measured in separate rooms, with a time
41 difference of a few minutes.

42 We used the data on serum glucose and low-density lipoprotein cholesterol (LDL-C) levels at
43 baseline. Diabetes mellitus was defined as the serum glucose level of ≥ 126 mg/dL and/or the use of antidiabetic
44 medications according to the standard diagnostic criteria (1). The participants were instructed to fast before
45 undergoing the health checkup. The HbA1c value was not used because it was not assessed during the health
46 checkups prior to March 2012. Hyperlipidemia was defined as the serum LDL-C level of ≥ 140 mg/dL and/or the
47 use of antihyperlipidemic medications according to the American guidelines (2).

48 There were missing values for serum glucose levels, serum low-density lipoprotein cholesterol levels,
49 current smoking and drinking status, regular exercise, and antihypertensive medication use. The percentage of
50 missing values across the six variables varied between 34.0 to 35.3% (out of 5,479 records), and 9.5 to 11.4%
51 (out of 2,045 records) in the analysis at 1 and 4 kHz, respectively. A total of 1,992 (36.4%) and 247 (12.1%)
52 records were incomplete, respectively. A compact display of patterns of missingness with covariates is presented
53 in Tables S1 and S2 for the analysis at 1 kHz and 4 kHz, respectively.

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55 **Statistical Analysis**

56 The baseline characteristics of the participants according to their SBP were presented as the mean
57 values of continuous variables and proportions of categorical variables. A trend test using general linear and
58 logistic regression analysis was performed to compare the baseline variables and proportions according to SBP.

59 A multivariable generalized linear mixed model was constructed to evaluate the effects of SBP on
60 repeated measures of hearing threshold with first-order autoregressive modeling. We constructed an age- and

61 sex-adjusted and a multivariable model to adjust for the variables based on the risk factors of HI reported before
62 (3). The multivariable model was adjusted for age (50–54 and 55–59 years), sex, BMI (<18.5, 18.5–20.9, 21.0–
63 22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, and ≥ 30.0 kg/m²), antihypertensive medications (no, yes), diabetes (no,
64 yes), hyperlipidemia (no, yes), current smoking habits (no, yes), alcohol intake (no, occasional, everyday), and
65 exercise habits once or more times per week (no, yes).

66 The missing values of the covariates at baseline were processed using multiple imputation methods.
67 Incomplete variables were imputed under fully conditional specification (FCS) that could handle missing
68 categorical data (4). Multiple regression model included parameters of exposure (SBP), adjusted variables, and
69 auxiliary variables (cohort enrollment year and type of participants [contractual workers of companies, staff of
70 [Author’s institution] and the affiliated facilities, and private individuals]). There were more missing data among
71 participants who enrolled earlier and were staff of [Author’s institution] (including the affiliated nursing
72 facilities); therefore, we added these variables to the regression models for multiple imputation. The results
73 across 100 imputed datasets were combined by taking the average (5), and standard errors were adjusted to
74 reflect both within-imputation variability and between-imputation variability, according to Rubin’s rule (6).

75 In addition, an alternative modeling strategy, Markov chain Monte Carlo (MCMC), was conducted
76 (7), and the results were compared with those obtained from the FCS method. When using the MCMC method,
77 we rounded the continuous imputations to the nearest allowed integer values.

78 Two-tailed *p*-values were obtained from the statistical analysis, with a *p*-value <0.05 considered as
79 statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC,
80 USA).

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References

- 83 1. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in
84 Diabetes–2018. *Diabetes Care* 2018;41:S13–S27.
- 85 2. Stone NJ, Robinson JG, Lichtenstein AH, et al.; American College of Cardiology/American Heart
86 Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood
87 cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of
88 Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129:S1–45.
- 89 3. Walling AD, Dickson GM. Hearing loss in older adults. *Am Fam Physician* 2012;85:1150–6.
- 90 4. van Buuren S. Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification.

- 91 *Stat Methods Med Res* 2007;16:219–42.
- 92 5. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for
93 practice. *Stat Med* 2011;30:377–99.
- 94 6. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Wiley: New York, USA, 1987.
- 95 7. Schafer JL. *Analysis of incomplete multivariate data*. Chapman & Hall: London, UK, 1997.

TABLE S1. *A compact display of patterns of missingness with covariates among participants in the analysis at 1 kHz*

Number of participants (N=5,479)	Antihypertensive medications	Diabetes	Hyperlipidemia	Current smoking habits	Alcohol intake	Exercise habits
3,487	X	X	X	X	X	X
10	X	X	X	X	X	
60	X	X	X	X		X
4	X	X	X	X		
1	X	X	X		X	X
1	X	X		X	X	X
6	X		X	X	X	X
38	X			X	X	X
10	X					
1			X			
2				X	X	
1,859						

An "X" indicates the presence of data, and a blank indicates missing data.

TABLE S2. *A compact display of patterns of missingness with covariates among participants in the analysis at 4 kHz*

Number of participants (N=2,045)	Antihypertensive medications	Diabetes	Hyperlipidemia	Current smoking habits	Alcohol intake	Exercise habits
1,798	X	X	X	X	X	X
4	X	X	X	X	X	
9	X	X	X	X		X
1	X	X		X	X	X
2	X		X	X	X	X
28	X			X	X	X
9	X					
2				X	X	
192						

An "X" indicates the presence of data, and a blank indicates missing data.

TABLE S3. Effects of variables in the generalized linear mixed model on hearing threshold at 1 kHz and 4 kHz under fully conditional specification (FCS) and Markov chain Monte Carlo (MCMC) to impute missing variables

Frequency	Analysis at 1 kHz (N=5,479)			Analysis at 4 kHz (N=2,045)		
	Parameter estimates (95% CI)	Standard error	p-value	Parameter estimates (95% CI)	Standard error	p-value
Age- and sex-adjusted model						
Intercept	30.0 (29.9 to 30.2)	0.1	<.001	30.6 (30.0 to 31.2)	0.3	<.001
SBP (mmHg)	-0.0005 (-0.0020 to 0.0010)	0.0007	0.50	-0.0039 (-0.0084 to 0.0007)	0.0023	0.09
Year	-0.046 (-0.084 to -0.008)	0.019	0.02	-0.39 (-0.57 to -0.21)	0.09	<.001
SBP (mmHg) * Year	0.00078 (0.00047 to 0.00108)	0.00016	<.001	0.0045 (0.0030 to 0.0059)	0.0007	<.001
Multivariable model under FCS ^a						
Intercept	30.1 (29.9 to 30.3)	0.1	<.001	30.4 (29.8 to 31.0)	0.3	<.001
SBP (mmHg)	-0.0009 (-0.0024 to 0.0007)	0.0008	0.28	-0.0045 (-0.0093 to 0.0003)	0.0024	0.06
Year	-0.047 (-0.085 to -0.009)	0.019	0.02	-0.37 (-0.55 to -0.19)	0.09	<.001
SBP (mmHg) * Year	0.00080 (0.00049 to 0.00110)	0.00016	<.001	0.0042 (0.0028 to 0.0057)	0.0007	<.001
Multivariable model under MCMC ^a						
Intercept	30.1 (29.9 to 30.3)	0.1	<.001	30.4 (29.8 to 31.0)	0.3	<.001
SBP (mmHg)	-0.0008 (-0.0024 to 0.0007)	0.0008	0.28	-0.0043 (-0.0091 to 0.0005)	0.0024	0.08
Year	-0.047 (-0.085 to -0.009)	0.019	0.02	-0.38 (-0.56 to -0.20)	0.09	<.001
SBP (mmHg) * Year	0.00080 (0.00049 to 0.00110)	0.00016	<.001	0.0044 (0.0029 to 0.0058)	0.0007	<.001

CI, confidence interval; FCS, fully conditional specification; MCMC, Markov chain Monte Carlo; SBP, systolic blood pressure

^a Adjusted for age, sex, body mass index, antihypertensive medications, diabetes mellitus, hyperlipidemia, current smoking habits, alcohol intake, and exercise habits