The impact of cardiovascular diseases on hearing deterioration: a 13-year follow-up study

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Acronyms and abbreviations: ARHI: Age-related hearing impairment, CVD: cardiovascular disease, PTA: Pure-tone average, HI: Hearing impairment, HL; Hearing level, BEHL: Better ear hearing level, WEHL: Worse ear hearing level, CI: Confidence interval

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Abstract

Objective. To study the impact of cardiovascular diseases (CVDs) on hearing deterioration among ageing adults in a longitudinal setting. Furthermore, to describe the pure tone threshold changes at the 0.125–8 kHz frequency range over 13 years.

Design. A population-based follow-up study.

Study sample. A random sample of 850 adults, of whom 559 participated in the follow-up study. Otological examination, a structured interview and pure tone audiometry were conducted. Multivariate regression models were used to estimate the effect of CVD (participants had at least one cardiovascular condition) on hearing deterioration of the better ear hearing level (BEHL), defined as a change in the pure-tone average (PTA) of the frequencies 0.5, 1, 2 and 4 kHz and separately at the lower (0.125, 0.25 and 0.5 kHz) and higher (4, 6 and 8 kHz) frequencies.

Results. In the multivariable adjusted analysis, the BEHL change at 13 years was 0.7 dB greater among participants with CVD (p=0.3). The mean BEHL change during the 13-year follow-up was 12.0 dB (95% CI 11.4–12.6) among all participants.

Conclusions. No significant association between CVD and hearing threshold changes was found.

Introduction

Hearing impairment (HI) is a highly prevalent condition among older adults, and the number of hearing-impaired adults is increasing (Olusanya, Davis, & Hoffman, 2019). Hearing thresholds tend to decline progressively with age (Gates & Cooper, 1991; Pearson et al., 1995). Based on cross-sectional studies, the deterioration of hearing starts gradually in early adulthood, increases remarkably with age, and affects more men than women (Cruickshanks et al., 1998; Davis, 1995). Many individual and environmental risk factors have been associated with age-related hearing impairment (ARHI), including genetics, lifestyle and health-related factors (Agrawal, Platz, & Niparko, 2009; Fransen et al., 2008).

Only a few earlier studies report hearing threshold changes over time at the population level. In the Framingham cohort, hearing threshold changes of 1,475 participants over six years were examined (Gates & Cooper, 1991). The participants were 58–88 years old at the baseline examination, and their age was 63–95 years at the follow-up. At lower frequencies (0.25–1 kHz), the threshold changes were greater among women, but no gender differences were found at higher frequencies (4–8 kHz). The rate of threshold change decreased with age at higher frequencies (Gates & Cooper, 1991). In a longitudinal study among adults aged 41–65 years, the deterioration of mean hearing thresholds was reported to be approximately 3 dB HL per decade among adults under 55 years of age and approximately 9 dB HL among adults over 55 years (Davis, Ostri, & Parving, 1991). In the Epidemiology of Hearing Loss Study (EHLS), 10-year longitudinal hearing threshold changes were reported among 2,130 adults aged 48–92 years (mean age 65.8) at baseline and 58–100 years (mean

age 72.7 years) at the 10-year follow-up. The mean rate of change was 0.5 to 1.5 dB HL/year, which accelerated with age (Wiley, Chappell, Carmichael, Nondahl, & Cruickshanks, 2008). It has been described that hearing deterioration begins at higher frequencies among young adults and progresses by age to lower frequencies (Kim, Lee, Moon, & Park, 2019; Lee, Matthews, Dubno, & Mills, 2005; Pearson et al., 1995).

In addition to age and the male sex, several other risk factors for HI have been found in cross-sectional studies. Many of them commonly have cardiovascular risk factors, such as smoking, diabetes (DM) and socioeconomic status (Fransen et al., 2008; Sommer et al., 2017), as well as hypertension (Agrawal et al., 2009; Gates, Cobb, D'Agostino, & Wolf, 1993). A recent cross-sectional study showed evidence of the association of a low cardiovascular risk score and better hearing at the population level (Curti et al., 2020). An association between cardiovascular diseases (CVDs) and HI has been found in some cross-sectional population-based studies (Gates et al., 1993; Gong et al., 2018; Tan et al., 2018; Torre, Cruickshanks, Klein, Klein, & Nondahl, 2005). In other studies, however, no association has been found (Helzner et al., 2011; Lohi, Hannula, Ohtonen, Sorri, & Mäki-Torkko, 2015; Nash et al., 2011). In a large Norwegian population-based study, the influence of CVD risk factors on hearing appeared to be small (Engdahl, Aarhus, Lie, & Tambs, 2015).

A longitudinal study design is superior if the interest is in the impact of risk factors on changes in hearing. Several risk factors in relation to the incidence of HI, such as socioeconomic status, history of a noisy job (Cruickshanks, et al., 2010), smoking, higher waist circumference, poorly controlled DM (Cruickshanks et al., 2015) and several ototoxic medications (Joo et al., 2020) have been reported in the EHLS. Kiely and coworkers (2012)

reported that hypertension was associated with the progression of HI, but heart attacks were not. However, a cross-sectional association between stroke and HI was reported (Kiely, Gopinath, Mitchell, Luszcz, & Anstey, 2012). In a retrospective longitudinal study by Kim et al. (2019), smoking increased the hearing threshold change (at 0.5–4 kHz), while a low level of low-density lipoprotein was associated with a smaller change. None of the studied cardiovascular risk factors (DM, smoking, age, sex, blood pressure) was associated with the progression of hearing in another longitudinal population-based study, but the follow-up time was only 4 years (Rigters et al., 2018). Few longitudinal population-based studies have addressed the impact of CVD on changes in hearing or the incidence of HI. Chronic diseases, such as CVD, hypertension and DM, had no influence on hearing threshold changes (Kim et al., 2019). In a European population-based study, CVD was associated with faster hearing deterioration, but the effect was small and was found only in middle-aged (43–62 years) adults (Linssen et al., 2014). CVD has been linked with accelerated hearing deterioration and low-frequency HI among older (>80 years) adults in a retrospective patient record study (Wattamwar et al., 2018).

Overall, no definitive conclusion of the effect of CVD on the acceleration of hearing deterioration can be drawn. Thus, the aim of the study was to describe hearing threshold changes in a 13-year follow-up in a population-based sample of adults living in or in the vicinity of the city of Oulu in northern Finland, and to investigate the effect of CVD on hearing deterioration among adults in a longitudinal setting.

Methods

Study sample

The study population was originally collected as a part of the European ARHI project (QLRT-2001–00331), a multicentre study that was designed to investigate environmental, medical, and genetic factors contributing to ARHI (Van Eyken, Van Camp, & Van Laer, 2007). A population-based random sample of persons born between 1938 and 1948, living in or in the vicinity of the city of Oulu, Finland, defined by postal code, was drawn. At baseline, invitation letters were mailed to 1,428 persons, of whom 858 agreed to participate. The baseline study population consisted of 850 adults: 383 men (45.1%) and 467 women. The baseline participants did not differ from nonparticipants by general health, smoking habits, or ear diseases, but the proportion of men was higher among the nonparticipants (55.8%) than participants (45.1%). Self-reported hearing difficulties were more common among participants (37.1%) than nonparticipants (21.5%) (Hannula, Mäki-Torkko, Majamaa, & Sorri, 2010). A total of 749 individuals who had attended the baseline study were alive at the enrolment in the follow-up phase. They were contacted by telephone for the follow-up examination. An invitation letter was mailed to 62 persons who could not be reached by telephone. An appointment was scheduled for those who agreed to participate. A more detailed description of sampling has been published earlier (Lohi, Ohtonen, Sorri, Mäki-Torkko, & Hannula, 2021).

Data collection

The baseline data were collected during the years 2003–2006. The follow-up data were collected during 2017–2018 according to a similar protocol. At the first step of the current follow-up study, a questionnaire was sent to the participants to fill out at home. In the questionnaire, their self-perceived hearing problems, medical history, and exposure to noise

were assessed. At the study appointment, the participants were interviewed by one of the researchers (VL) to avoid any misunderstanding of the items in the questionnaire. An otological examination was performed by an ENT surgeon (VL), including pneumatic otoscopy or otomicroscopy, tympanometry and ear wax removal when needed.

The presence of cardiovascular diseases was defined by self-report. The personal medical files were reviewed to check the medical history of the participants when necessary. The total CVD variable included a history of one or more of the following conditions: coronary heart disease, myocardial infarction, stroke, transient ischaemic attack, claudication, atrial fibrillation, valve problem or heart insufficiency. The CVD variable was defined based on the status at the follow-up examination. The current smoking status, the amount of daily smoked cigarettes and the duration of smoking in years were self-reported. The smoking status was classified by the total amount of smoking as pack-years, i.e., one pack-year defined as one pack of cigarettes a day for one year: 1) never smokers or less than 1 pack-year; 2) 1 to 19 pack-years; and 3) 20 or more pack-years. The weight of the participants was measured at the study appointment, and the height was self-reported, which enabled calculation of the body mass index (BMI). As a definition for obesity, BMI $\geq$30 kg/m^2 was used (Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults.1998). Socioeconomic status was defined by the participants' occupation at the baseline study according to Statistics Finland (1998). The same classification was used in the follow-up study. Exposure to noise was screened by questions on occupational, leisure time and firearm noise exposure as described previously (Hannula, Bloigu, Majamaa, Sorri, & Maki-Torkko, 2012). Briefly, a participant was defined as noise-exposed if he or she had a history of any of the following: working more than one year in a noisy environment; regular (more than once a week) exposure to intense sounds or noises at leisure time or exposure to gunfire noise for at least 100 rounds with

light weapons or 10 rounds with heavy weapons. Ear diseases were defined as a history of chronic otitis media, Ménière's disease, otosclerosis, radical ear operation or congenital HI. There were 10 participants (1.8%) with a history of ear disease in the better-hearing ear. Other otological risk factors included severe head trauma (leading to unconsciousness and contact with health care), ototoxic medication (amoniglycoside antibiotics or chemotherapy) or radiation therapy in the area of the head and neck, of which one or more were present in 64 (11.4%) of the participants at follow-up.

The audiometric examinations were conducted at the Hearing Centre of the Oulu University Hospital with clinical audiometers (Aurical Aud, Otometrics, Denmark), calibrated according to the International Organization for Standardization (ISO) 389–1 (ISO, 1998). Supra-aural TDH-39 P headphones with MX-41/AR cushions and Radioear NB-71 bone vibrators were used. Trained audiology assistants measured the pure-tone air conduction thresholds (0.125, 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz) and bone conduction thresholds (0.25, 0.5, 1, 2 and 4 kHz) according to the ISO 8253–1 standard (ISO 8253–1, 2010) in a sound-isolated booth (Puma Pro 45, Puma Soundproofing, Italy).

Definitions

Better ear hearing level (BEHL) was defined as the mean of the pure-tone air conduction thresholds (pure-tone average, PTA) at 0.5, 1, 2 and 4 kHz in the better-hearing ear. The lower frequency hearing level was defined as the mean of the pure-tone air conduction thresholds at 0.125, 0.25 and 0.5 kHz, and the higher frequency hearing level was defined as the mean of the thresholds at 4, 6 and 8 kHz (Stephens, 1996).

Analysis of non-participants

Of the 850 baseline participants, 291 did not participate in the follow-up study. Of them, 101 had died before the follow-up enrolment, 117 were contacted but were unable or unwilling to participate, and the remaining 73 could not be contacted. Generally, the non-participants were one year older than the participants. There was no difference in the presence of cardiovascular conditions at baseline or at the follow-up between the participants and non-participants who responded to the questionnaire. However, cardiovascular conditions at baseline were significantly more common (30.7%) among baseline participants who had died before the follow-up than among participants (11.7%, p=0.002). The prevalence of HI at baseline (BEHL0.5–4 kHz≥20 dB) was 24% among the follow-up participants and 27.4% among the non-participants. A more detailed comparison of the demographics and characteristics of the participants and non-participants has been reported earlier (Lohi et al., 2021).

Statistical analyses

Paired sample T tests were used for the crude estimates and confidence intervals (CI) of threshold changes. Missing audiogram data were imputed using the multiple imputation (MI) method. Fifty different datasets were created, and pooled results are presented for the change in BEHL and the lower and higher frequency hearing levels. The imputation was performed only for those who were alive at the time of follow-up. Two different multivariable adjusted linear regression models were used to analyse the impact of cardiovascular diseases on the deterioration of hearing. In Model 1, possible risk factors based on the literature were selected as covariates: age, sex, hypercholesterolemia, hypertension, diabetes, smoking, obesity, socioeconomic class, noise exposure, ear diseases and other otological risk factors. In Model 2, a directed acyclic graph (DAG,

www.dagitty.net) was used to select the adjusting covariates, and age, sex, hypercholesterolemia, hypertension, diabetes, smoking, obesity, and socioeconomic class were included accordingly. The DAG used in this study is presented in Supplementary Figure 1. All statistical analyses were performed using SPSS for Windows (IBM Corp., released 2017, SPSS Statistics for Windows, Version 26.0. Armonk, USA) software.

Ethical considerations

This study was planned and conducted according to the guidelines of the Finnish National Advisory Board on Health Care Ethics and approved by the ethical committee of North Ostrobothnia's hospital district. Written informed consent was obtained from all the participants. No financial compensation was provided for participation.

Results

Threshold changes in the right and left ears

The mean follow-up time counted from the baseline and follow-up audiogram dates was 13.4 years (13.0–15.2 years). In the right ear, the pure-tone threshold changes were smallest at the lower frequencies and increased at the higher frequencies. In the left ear, the decline was greatest at 4.0 kHz among men and at 4.0 and 6.0 kHz among women. The mean audiograms for men and women at baseline and at the follow-up are presented in Figure 1. The frequency-specific mean pure-tone threshold changes of follow-up participants in the right and left ears separately are presented in Table 1, and the figures with 95% CIs are presented in Supplementary Table 1. The mean $PTA_{0.5\text{-}4\ kHz}$ at the follow-up was 29.8 dB HL (median 27.5, SD 16.1) in the right ear and 30.4 dB HL (median 28.8, SD 14.3) in the left ear. The median and mean pure tone thresholds for men and women at baseline and at the

follow-up are presented in Supplementary Tables 2 and 3. Among all subjects, there was a 0.48 dB HL difference in the PTA $_{(0.5\text{-}4\ kHz)}$ change between the right and left ears (95% CI -0.05 to 1.07). The difference between the right and left ears was 1.69 dB HL in men (95% CI 0.17 to 3.2) and -0.27 dB HL in women (95% CI -1.59 to 0.85).

Average hearing changes at different frequency ranges

In Table 2, the better ear PTA changes according to sex and age at baseline are presented for BEHL and separately for the lower and higher frequencies. The mean deterioration rate of BEHL was 0.91 dB/year. The rate was 0.41 dB/year at the lower frequencies and 1.55 dB/year at the higher frequencies. There were no significant changes between men and women in the rate of change (p=0.2 at 0.5–4 kHz). The changes increased with age, from the lower to the higher frequencies among both sexes and age groups and were the smallest in younger women at the lower frequencies (3.5 dB HL) and highest in older women at the higher frequencies (23.7 dB HL). There were only minor differences between the MI analysis and the complete case analyses, and thus, the results of the MI analyses are presented only in the supplementary material (Supplementary Table 4).

Multivariable adjusted analysis of the impact of cardiovascular diseases

At least one cardiovascular disease was reported by 67 participants (12.0%) at baseline and by 210 participants (36.7%) at follow-up. Before adjustment, the BEHL change averaged over the frequencies 0.5, 1, 2 and 4 kHz was 1.3 dB greater among participants with CVD (95% CI 0.13–2.49) than without CVD during the follow-up period. After adjustment, the effect of CVD was only 0.7 dB HL. The effect of CVD is greater at lower frequencies but is still not statistically significant. The results of the two multivariate adjusted models in

different frequency ranges are presented in Table 3. The results obtained by both Model 1 and Model 2 were very similar.

Discussion

The impact of cardiovascular diseases

We found no association between CVDs and hearing deterioration; after adjusting for covariates, the effect was only 0.6–0.8 dB HL in those 13 years. The effect of CVDs was quite constant across the frequency scale and, related to the smaller threshold changes, more pronounced at the lower frequencies but still neither statistically nor clinically significant. Similar findings have been found in an Australian longitudinal, population-based study, in which stroke or diabetes were not associated with a faster decline in hearing thresholds (Kiely et al., 2012). In another relatively large, population-based European study, CVD was reported to be associated with hearing deterioration rate in middle-aged adults (43–62 years), but its effect was small (Linssen et al., 2014). In these two studies, the effect of CVD was studied only at limited frequencies, 1–4 kHz in the study of Linssen et al. (2014) and 0.5–4 kHz in the study of Kiely et al. (2012). Furthermore, in a Korean longitudinal study in which CVD was not associated with hearing threshold changes, lower frequencies were not separately addressed (Kim et al., 2019). The results of the retrospective patient record study of Wattamwar et al. (2018) found a 10-fold effect of CVD on the hearing threshold change compared to the present study; the mean decline of low-frequency PTA (0.5, 1 and 2 kHz) was 0.72/year higher among participants with CVD compared to disease-free controls (Wattamwar et al., 2018). However, the results are not comparable to the present study because the participants of that study were remarkably older (80–106 years, mean age 89 years) and the sample was not population-based. In our study, the duration or onset of CVD was not considered, and the effect of CVD may not be found if the disease is recently

manifested. Taken together, the influence of CVD on hearing deterioration appears negligible if not nonexistent.

Hearing threshold changes and the rate of change

In general, the average deterioration rate of BEHL (0.5–4 kHz) was 0.91 dB/year, which is similar to the results of an earlier, larger population-based study (Kiely et al., 2012) and in line with other previous studies (Davis et al., 1991; Kim et al., 2019; Linssen et al., 2014; Wiley et al., 2008). The pattern of the threshold changes in different frequencies in our study is also in agreement with previous reports: in the EHLS, in the 60–69-year-old subgroup, the mean rate of change was approximately 0.75 dB HL/year at 0.5 kHz and 1.4 dB HL/year at 8 kHz among men and 0.75 dB HL/year at 0.5 kHz and 1.75 dB HL/year at 8 kHz among women (Wiley et al. 2008). Furthermore, there are similar results in the Rotterdam study, in which the average decline of hearing was 0.29 dB HL/year in the low (0.25, 0.5 and 1 kHz), and 1.35 dB HL /year in the high (2,4 and 8 kHz) frequencies (Rigters et al., 2018).

Effect of age

According to previous studies, the rate of hearing threshold change begins to slow down at higher frequencies in advanced age, after 80 years (Gothberg et al., 2019; Wiley et al., 2008). In our study, the participants were not older than 80 years at the end of the follow-up, and no slowing of hearing deterioration was detected; the threshold changes were greater among older participants in both sexes. This agrees with the results of EHLS in the corresponding age group (60 to 69 years) (Wiley et al., 2008). However, the maximum difference between the age groups was not more than 5.1 dB HL in 13 years seen at the higher frequencies among women. Generally, the differences between the age groups are smaller among men than among women.

Sex differences

The threshold changes were greater among men in the younger age group in all frequency ranges and among women in the older age group, which is in line with the study of Lee et al. (Lee et al., 2005). In the Baltimore study of ageing (BLSA), Pearson et al. (1995) found that the longitudinal rate of hearing decline was more than twice as rapid in men as in women at most ages and frequencies (Pearson et al. 1995). In contrast, in our study, the gender differences in the rate of threshold change were not significant. Furthermore, the absolute threshold changes in the corresponding age group were greater in our study than in the BLSA. However, the results are not comparable to our study because of the screened population in BLSA (Pearson et al., 1995). Significant but relatively small sex differences were also found in the study of Linssen et al. (2014), in which the hearing deterioration rate was 1.3 dB HL/decade higher in middle-aged men and 1.8 dB HL/decade higher in older men than in women. It has been speculated that menopause could be linked with HI among women (Svedbrant, Bark, Hultcrantz, & Hederstierna, 2015). However, no overall association between menopause and self-reported HI was found after adjusting for age in a larger, prospective study (Curhan et al., 2017).

Strengths and limitations

The strength of this study includes an unscreened, population-based sample and longitudinal design with good participation in the follow-up study. In addition, proper audiological measurements, otological examinations and the possibility of checking personal medical files increase the reliability of the study. One limitation of the study is that the participants were seen and examined only twice. Many of the issues, such as smoking and noise exposure, were based on self-report and therefore the possible cause of recall bias, even

though all the issues were verified in the interview. Furthermore, the age range for this study is rather small; the findings are not generalizable to other age groups or nationalities.

Conclusion

No significant association between CVD and hearing deterioration was found in this population-based follow-up study. We found that in this sample of 54–66-year-old adults, hearing deterioration was accelerated by age; hearing deterioration was smaller at lower frequencies and increased to higher frequencies. No significant sex differences in the hearing threshold changes were detected.

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Disclosure statement

The authors report no conflicts of interest. All responsibility for the content and writing of the paper is taken by the authors alone.

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Figure 1.

Audiograms for men and women with mean air conduction thresholds at the baseline and at the follow-up.

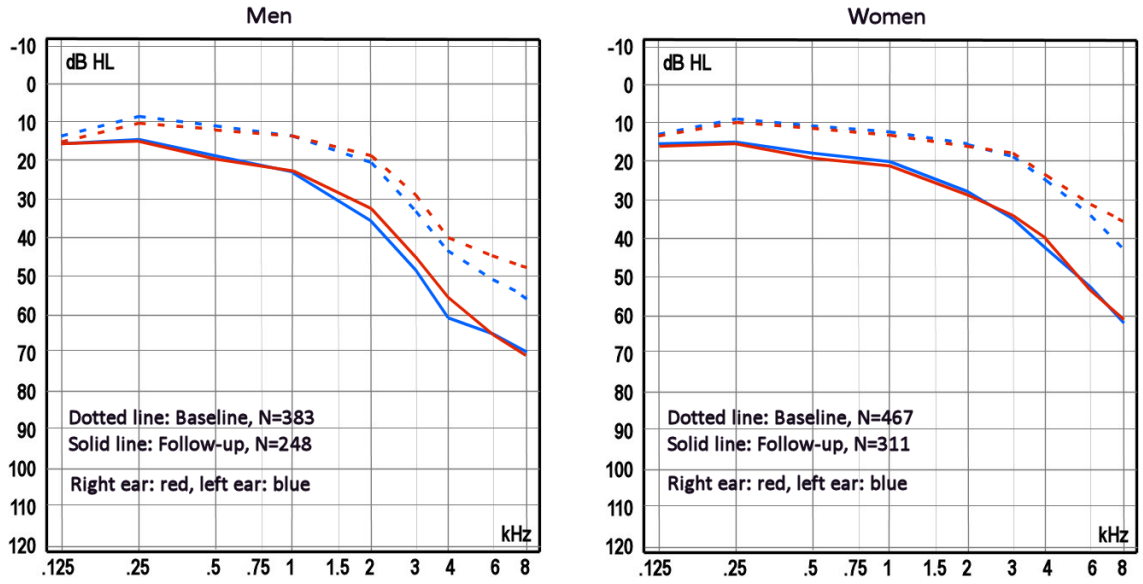

Table 1. Mean pure-tone threshold changes (dB HL) of follow-up participants at each frequency in the right and the left ear in 13-year follow-up. Figures with 95% confidence intervals presented in Supplementary Table 1.

			Mean change, dB HL								
Sex	*Ear*	*kHz*	0.125	0.25	0.5	1.0	2.0	3.0	4.0	6.0	8.0
Men	R		1.6	5.7	8.8	9.4	14.3	17.5	18.0	22.9	24.6
	L		3.2	6.3	9.6	10.5	16.1	17.1	18.6	16.6	16.2
Women	R		3.1	6.3	9.3	8.9	13.5	16.9	17.6	23.0	26.1
	L		4.0	6.0	8.6	8.9	14.1	17.3	19.5	21.1	21.0
All	R		2.4	6.0	9.1	9.1	13.8	17.2	17.8	23.0	25.5
	L		3.6	6.1	9.1	9.6	15.0	17.2	19.1	19.1	18.9

Table 2. Changes of hearing thresholds (mean and 95% confidence interval, CI) for different frequency ranges in the better ear in 13-year follow-up according to age at baseline and sex.

		Mean change, dB HL (95% CI)		
Baseline age	*Sex (N)*	*0.125, 0.25 and 0.5 kHz*	*0.5, 1, 2 and 4 kHz*	*4, 6 and 8 kHz*
54-60 years	*Men (108)*	4.9 (3.9 to 5.9)	11.5 (10.3 to 12.8)	18.9 (17.0 to 20.8)
	Women (150)	3.5 (2.6 to 4.4)	9.8 (8.7 to 10.8)	18.6 (16.8 to 20.3)
	All (258)	4.1 (3.3 to 4.8)	10.5 (9.7 to 11.3)	18.7 (17.5 to 20.0)
61-66 years	*Men (140)*	5.5 (4.5 to 6.6)	13.0 (12.0 to 14.1)	21.2 (19.3 to 23.0)
	Women (161)	7.2 (6.3 to 8.1)	13.5 (12.4 to 14.5)	23.7 (22.0 to 25.5)
	All (301)	6.4 (5.7 to 7.1)	13.3 (12.5 to 14.0)	22.5 (21.3 to 23.8)
All	*Men (248)*	5.2 (4.5 to 6.0)	12.4 (11.6 to 13.2)	20.2 (18.9 to 21.5)
	Women (311)	5.4 (4.8 to 6.1)	11.7 (10.9 to 12.5)	21.3 (20.0 to 22.5)
	All (559)	5.3 (4.9 to 5.8)	12.0 (11.4 to 12.6)	20.8 (19.9 to 21.7)

Table 3. The results of the multivariable adjusted regression analysis of the impact of cardiovascular diseases[a] on the better ear hearing deterioration in the 13-year follow-up study

Frequencies	*Model*	*Effect of CVD[b] (dBHL)*	*95% CI*	*P value*
0.125, 0.25 and 0.5 kHz	1	0.84	-0.26 to 1.93	0.13
	2	0.82	-0.27 to 1.91	0.14
0.5, 1, 2 and 4 kHz	1	0.68	-0.57 to 1.93	0.28
	2	0.70	-0.55 to 1.95	0.27
4, 6 and 8 kHz	1	0.63	-1.39 to 2.65	0.54
	2	0.58	-1.44 to 2.59	0.57

[a] coronary heart disease, history of myocardial infarction, stroke or transient ischemic attack, claudication, valve problem, atrial fibrillation of heart insufficiency
[b] Regression coefficient
Model 1: Adjusted with age, sex, hypercholesterolemia, hypertension, diabetes, smoking, obesity, socioeconomic class, noise exposure, ear diseases and other otological risk factors
Model 2: Adjusted with age, sex, hypercholesterolemia, hypertension, diabetes, smoking, obesity and socioeconomic class