

Short title

Progression of Hearing Loss in the Aging Population.

Full title

Progression of Hearing Loss in the Aging Population - repeated auditory measurements in the Rotterdam Study.

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Declaration of interest

None.

Funding

This work was supported by a grant from the Heinsius Houbolt foundation and a grant from Cochlear.

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Progression of Hearing Loss in the Aging Population

repeated auditory measurements in the Rotterdam Study

ABSTRACT

We quantified changes in the auditory acuity of 675 aging adults (mean age 71.1 years old, 52.0% female, mean follow up 4.4 years \pm 0.2) of an ongoing cohort study with a pure-tone audiogram and a speech-in-noise test. Generalized estimating equation models were used to study the association between hearing loss and the progression with age, sex, education, cognition, BMI, blood pressure, having type 2 diabetes mellitus, cholesterol ratio, smoking and alcohol consumption. The mean progression of hearing loss was 0.29 and 1.35 decibels per year (low / high frequencies). Progression of hearing loss was associated with baseline hearing thresholds. Besides, the presence of type 2 diabetes, smoking, age, sex and time were associated with worse hearing at baseline, but there was no statistical evidence that the tested determinants were associated with progression of hearing loss. This finding indicates that the 4-year progression of hearing loss in older adults in this study is not influenced by the measured determinants. More research with multiple follow up rounds is desired.

Keywords: Age-related hearing loss, aging population, hearing impairment, longitudinal research, presbycusis, progression, speech perception.

INTRODUCTION

Age-related hearing loss affects over a billion people worldwide [GBD, 2016] and its prevalence keeps rising due to aging of the population [Olusanya et al., 2014]. As the fourth leading cause of years lived with disability in developed countries [GBD, 2016], hearing loss has a major impact on daily life, and is associated with high healthcare costs.

The nature of hearing loss in older adults is progressive [Cruickshanks et al., 2010]. From the fifth decade onwards, hearing thresholds and speech understanding in noise gradually decline. Multiple determinants are thought to influence the onset and severity of hearing loss in older adults, namely demographic factors such as age, sex and social economic status [Agrawal et al., 2008]; medical factors such as cardiovascular disease, cognition, diabetes mellitus, cholesterol level and obesity [Gopinath et al., 2010; Helzner et al., 2011; Akinpelu et al., 2014; Taljaard et al., 2016; Dhanda and Taheri, 2017];

life style related factors such as noise exposure, smoking and an inverse correlation for alcohol consumption [Agrawal et al., 2008; Dawes et al., 2014; Rigters et al., 2016; Lin et al., 2017]; and genetic susceptibility [Hoffmann et al., 2016]. The rate of the progression of hearing loss varies widely among people of the same age [Gates and Mills 2005]. The decline of pure-tone thresholds over time has been found associated with several factors such as age, being male or female, blood pressure, obesity, having diabetes, cognitive impairment and manual occupation [Brant et al., 1996; Mitchell et al., 2009; Kiely et al., 2012; Linssen et al., 2014]. When reviewed critically, some studies that claim to address associations on progression, in fact addressed the incidence of hearing loss [Cruickshanks et al., 2015]. In general, previous studies lack the combination of 1) a representative aging population with a wide range of hearing (instead of a group of hearing-impaired compared to a group of normal hearing participants), where, 2) auditory acuity (thresholds and speech perception) as well as the possible determinants were measured and, 3) sufficient statistical methods were used.

Knowing which patients are at risk of more rapid deterioration of hearing acuity could influence counseling, rehabilitation and possible treatment of the underlying condition. The purpose of this study is to identify if and to what extent the progression of hearing loss in older adults over time is associated with potentially relevant determinants.

MATERIALS AND METHODS

Study population

This study is embedded in the Rotterdam Study, an ongoing population-based prospective cohort study designed to investigate the health of aging people [Hofman et al., 2015]. The population consists of inhabitants aged 55 years and above of the Ommoord district in the city of Rotterdam, the Netherlands. In 2011, hearing assessment was implemented in the study protocol and participants are invited for reassessment approximately every 4 years. In 2015 the first group of participants was invited for their second hearing assessment. For the current study, we included participants with two hearing assessments (N = 722 from 5,762). Those who had been reassessed within less than 3 years (N = 18) and those with conductive hearing loss on the best hearing ear (N = 29) were excluded. This resulted in a total number of 675 participants. Included participants did not significantly differ in age, sex and mean hearing loss from participants with one hearing assessment.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus University Medical Center and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Screening Act: Rotterdam Study. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Hearing assessment

Participants were tested by a single qualified professional in a soundproof booth at the research center. TDH-39 headphones and a clinical audiometer (Decos audiology workstation, version 210.2.6 with AudioNigma interface) were used. A pure-tone audiogram and speech-in-noise test were performed. First, pure-tone thresholds were measured according to the ISO-standard 8253-1 [ISO 2010]. Air conduction (0.25, 0.50, 1, 2, 4 and 8 kilo Hertz, (kHz)) and bone conduction (0.5 and 4 kHz, due to limited time) were measured for both ears. Masking was done according to the method of Hood [Hood, 1960]. Bone conduction thresholds at 4 kHz were +10 dB adjusted afterwards (Margolis et al. 2013). The best hearing ear was determined by calculating the mean threshold over all frequencies. If hearing was equal between both ears, alternately right or left was chosen. On the best hearing ear, we calculated low (mean of 0.25, 0.50 and 1 kHz), speech (mean of 0.50, 1, 2 and 4 kHz), and high (mean of 2, 4 and 8 kHz) frequency hearing thresholds to determine the low-, speech- and high frequency hearing loss. To eliminate clinically relevant conductive hearing loss, test results of participants with an air-bone-gap of 15 dB or more were excluded from the analyses.

Subsequently, a simplified speech-in-noise test was done to quantify the speech recognition ability in noise. We performed the digits-in-noise (DIN) test on the best hearing ear [Koole et al. 2016]. Participants repeated digit triplets in an automated adaptive procedure, while the signal to noise ratio was changed according to the correctness of the answer. This resulted in a speech reception threshold which represents a speech in noise ratio for 50% correctly repeated triplets. A higher threshold means a worse ability of understanding speech in noise. After an preliminary evaluation of our hearing data, supra-threshold noise levels were changed from 55 dB at baseline to 65 dB during follow up. To avoid confounding with the peripheral hearing level, we additionally adjusted for the high frequency hearing thresholds in the subsequent analysis concerning the DIN test.

Progression of hearing loss was defined as devaluation of hearing thresholds from baseline to reassessment.

Determinants

Information on the potentially relevant determinants was acquired through a home-interview, physical examination, and blood sampling at baseline. Educational level was classified as having completed primary, secondary or higher schooling. Cognition was defined as the score on the Mini-Mental State Examination (MMSE). Body mass index (BMI) was calculated through weight and length. Systolic blood pressure was measured twice on the right brachial artery with the participant in a sitting position and in between a resting period of 5 minutes. The mean of the two values was used. Cases of type 2 diabetes were identified from general practitioners' records. If we could not retrieve this information, diabetes mellitus was considered present if glucose measurement was abnormal or if the participant used antidiabetic drugs. Abnormal glucose measurement was defined as fasting glucose 7mmol/L or more, or (if unavailable) as non-fasting glucose 11mmol/L or more. Cholesterol ratio was calculated as the quotient of serum total-cholesterol and high-density cholesterol. Smoking was classified as never, former or current. Alcohol consumption was categorized as none-drinker, light consumer (1 unit of alcohol per day for women and 1-2 units of alcohol per day for men) or above average consumer (more than 1 unit of alcohol per day for women and more than 2 units of alcohol per day for men) [Dawson and Room, 2000].

Statistics

To examine the characteristics of the study population, we calculated mean and standard deviation or percentage for all demographics. In the first analysis we calculated the association between baseline thresholds and the progression of hearing loss using a linear regression model, accounting for the different participant demographics. In a second analysis we used generalized estimating equations, to assess the effect of the different determinants on the progression of hearing loss [Zeger et al., 1988]. Population-average progression was defined as the main effect of time. To study the differences in progression of hearing loss between subgroups of the population, we allowed for interactions between time and all the determinants. Separate generalized estimating equation models were used for each of the hearing outcomes: the low, speech, and high frequency hearing thresholds and the outcome of the DIN-test; the speech reception threshold (SRT). To account for the correlation between measurements coming from the same subject we assumed an exchangeable correlation structure. We started by specifying an elaborate model including the main effects of all the determinants as well as higher order

terms such as interactions of baseline determinants with time and a quadratic effect of age. The higher order terms were then tested using multivariate Wald tests. A p -value of 0.05 or less was considered significant. All higher order terms were not found to be significantly different from zero and thus were dropped from the final models. The models including the higher order terms are shown in Table 1. of the Supplementary Material. Missing data were assumed to be missing completely at random. Analyses were performed using R 3.4.1. [R Core Team] and package geepack 1.2-1 [Yan, 2002; Yan and Fine, 2004; Hølsgaard et al., 2016].

RESULTS

Characteristics of the study population

A total of 650 complete cases were analyzed. Mean (SD, range) age at baseline was 71.1 (4.1, 66 - 87) years and 52% were females. Mean (range) follow up was 4.4 (3.3 - 5.1) years. All relevant characteristics of the study population are displayed in Table 1.

Progression of hearing loss

The difference in hearing thresholds was large (95% confidence interval at baseline for the mean threshold of lower frequencies 6.7;36.7 dB, of higher frequencies 18.3;68.3 dB). Pure-tone thresholds at baseline were worse for higher than for lower frequencies and thresholds worsened with each age category (Figure 1). The prevalence of age-related hearing impairment according to the WHO (pure-tone audiogram 0.5, 1, 2 and 4 KHz > 25 dB loss at best hearing ear) at baseline was 48.5%. The prevalence rose with each age category (respectively 38.8% for 66-69 years old, 53.1% for 70-79 years old, and 81.8% for 80-87 years old). At follow up this was 61.4% (53.6%, 65.5%, 84.8%).

Figure 2 shows the mean threshold at baseline in relation to the mean threshold at follow up, again displayed for the three age categories. All participants left and above of the drawn line showed progression of hearing loss. An increase in hearing thresholds - progressive hearing loss - was present for 512 participants (78.8%). The average decline of hearing loss was 0.29 dB per year in the low frequencies and 1.35 dB per year in the high frequencies. The progression was significantly associated with the baseline thresholds. For the lower frequencies an effect estimate of -0.07 dB per 4 years of follow up (p -value 0.010) was found and for the higher frequencies an effect estimate of -0.06 dB per 4 years of follow up (p -value 0.002), after correcting for age, sex, and the other determinants. In other

words, for approximately every 16 dB elevation of the baseline threshold, 1 dB less progression in the follow up period was expected.

Determinants

Using the full model specification, none of the interaction terms with time was found statistically significant at the 0.05 significance level. That is, there was no statistical evidence to support a difference in progression of hearing loss by the determinants investigated in this study. The interaction terms were therefore dropped from the final generalized estimating equation models. Table 2 displays the results of the final models for the low, speech and high frequency thresholds, as well as for the SRT. The initial, full models can be found in the Supplementary material.

Worse hearing thresholds in the low frequencies were associated with time, aging, being of female sex and being a current smoker. Increase of BMI and having type 2 diabetes were border significant. Worse hearing thresholds in the speech and high frequencies were associated with time, aging, being of male sex, having type 2 diabetes mellitus and being a current smoker.

Worse hearing on the SRT was inversely associated with time. Thus, speech reception seemed to improve over time. Furthermore, the SRT was associated with age, being of female sex and having type 2 diabetes.

The implications of our outcomes are visualized in Figure 3 by means of progression lines for high frequency hearing loss over time for different groups of participants. Smokers with diabetes mellitus had initial higher pure-tone losses at baseline (both males and females) but the progression of hearing loss in both groups was equal. The progression of hearing loss was also equal for males and females.

DISCUSSION

This study showed that the progression of hearing loss over a short time was not affected by age, sex, educational level, cognition, BMI, systolic blood pressure, presence of type 2 diabetes mellitus, cholesterol ratio, smoking and alcohol consumption. On the other hand, higher initial hearing thresholds had a decelerating effect on the progression rate. A baseline difference of approximately 16 dB resulted in 1 dB less progression over the 4 years of follow up, which effect is substantial in view of the average 1.35 dB decline of hearing loss per year.

Previous studies have reported inconsistent effects of the initial hearing level on the rate of progression. In line with our results, poorer baseline thresholds for the higher frequencies (4 - 8 kHz) were found to be associated with less progression in hearing loss [Gates and Cooper, 1991]. In that same study no effect of lower frequencies (0.25 - 1 kHz) was found. A similar result was also found in a study in which the progression of hearing loss was defined as a deterioration of >5 dB on 0.5 - 4 kHz [Cruikshanks et al., 2003]. In contrast, worse hearing thresholds were associated with a faster decline in another large cohort-based study [Linssen et al., 2014]. The follow up period in that study was longer (12 years), which could explain different findings. However, the authors presented only the results of the univariate analysis between progression and baseline thresholds, while we presented ours after correcting for age and sex. Because their study population included far younger participants than ours (24.0 - 83.7 years), the found effect might also have been a consequence of a different aetiology of hearing loss, for example a genetic cause.

In our second analysis, the generalized estimating equation models, none of the determinants had an effect on the progression of hearing loss according to the *p*-value chosen to test statistical significance, other than the elapse of time itself. Remarkably, the time-effect found on the SRT was inverse. Time seemed to have an inhibitory effect on speech perception loss. This can be ascribed to having adjusted the DIN-test after a first cross-sectional evaluation of our hearing data [Koole et al., 2016]. To reduce the confounding effect with pure-tone thresholds, supra-threshold noise levels were adjusted from 55 dB at baseline to 65 dB during follow up, to reduce the confounding effect with pure-tone thresholds. Age had no significant effect on the progression of hearing loss. This is surprising, as the ISO-standard [ISO, 2010] uses a model with a consistently increasing progression of hearing loss with age, which is in line with several studies that show accelerated progression with higher age [Kiely et al., 2012; Linssen et al., 2014]. These studies were able to use linear mixed models because they had multiple audiometric measurements. Because in the present study only two audiometric measurements per participant available, our analysis was restricted to generalized estimating equations rather than mixed-effect models. Still, the time span between the two measurements may have been too short to identify a significant difference in progression. Furthermore, due to interpretation purposes and the endogenous nature of some of the exposures only the baseline values of the determinants were used as exposure variables.

Another difference with the studies of Kiely et al. and Linssen et al. is that our study population was older and thus more prone to a higher prevalence of age-related hearing loss. In older adults not only the effect of aging itself, but also a ceiling effect has been described: the more the loss of high frequency hearing, the less the rate of progression, possibly because a maximum loss was being reached [Brant and Fozrad, 1990; Wattamwar et al., 2017]. Therefore, we found more progression in the lower than in the higher frequencies. With an average age of 90 years, the study population of Wattamwar et al. was much older than our population, but it may well be that this stagnation of progression already is apparent at an earlier age, which may counteract a possible accelerated progression of hearing loss at higher ages as suggested by the ISO-standard.

Like age, also sex was not associated with the progression of hearing loss. This is in line with the adaptation of the new ISO-standard [ISO, 2017], in which sex differences are much smaller than in the older version [ISO, 2010]. We did find that sex was associated with the onset of hearing loss. Worse hearing thresholds in the lower frequencies were associated with being female and worse hearing in the speech and higher frequencies was associated with being male. Former cross-sectional studies found that women to have better high frequency hearing and that men have better low frequency hearing [Rigters et al., 2016]. This is possibly explained by the assumption that men are at higher risk of noise-induced hearing loss.

Because age-related hearing loss is thought to be a risk factor for the onset of dementia [Livingston et al., 2017], we studied the risk of developing dementia using poor performance on the DIN-test. Prior studies mainly focused on peripheral hearing loss (pure-tone audiometry), while we hoped with the DIN to reflect the higher auditory function. Dementia was stated as a MMSE score of 26 or lower and we calculated the odds ratio of the onset of dementia according to a worse performance on the DIN-test using a univariable logistic regression model, due to the fact that only 40 of the 559 non-demented at baseline developed dementia (7.2%). We found an odds ratio for dementia according to worse performance on the DIN-test of 1.05 (CI 0.99;1.12) with a *p*-value of 0.065, however this result should be looked at with care, since other baseline characteristics were not taken into account for this analysis. Some studies identified determinants that had an effect on the progression on hearing loss, such as a lower cognitive impairment, hypertension, having performed manual occupation and waist circumference [Kiely et al., 2012, Linssen et al., 2014]. Still, all effects were very small and may only become apparent after longer time.

Although in the present study type 2 diabetes and smoking were not associated with the progression of hearing loss, they were associated with the onset of age-related hearing loss. We found a significant effect regardless of the correction for cardiovascular confounders. This association of type 2 diabetes [Akinpelu et al., 2014] and smoking [Dawes et al., 2014; Chang et al., 2016; Rigters et al., 2016] with the prevalence of hearing loss in older adults was shown before. Possible hypotheses on the underlying pathogenesis of diabetes or smoking and hearing loss could be microangiopathy of the stria vascularis [Fukushima et al., 2006], neuropathy or mitochondrial damage [Helzner and Contrera, 2016]. For diabetes we found no significant effect in the lower frequencies and a larger effect in the higher frequencies when compared to the speech frequencies. This could indicate a vascular cause taking into account that the base of the cochlea is more vascularized than the apex and thus has a greater blood supply. The higher frequencies may therefore be more affected by microangiopathy [Shi, 2011].

One of the limitations of this study is that with two measurements per subject the statistical modeling options for studying the progression of hearing loss were limited (e.g. mixed-effects models with random slopes are not feasible). We therefore used generalized estimation equation models to fit the data best [Zeger et al., 1988]. With more follow up rounds planned we expect to report on this in the future. Another limitation was the short follow up time. We consider our results therefore to reflect on the short-term effects of hearing loss. Also we did not have information on noise exposure. Although in previous research no relation between noise-induced hearing loss and the progression of hearing loss was found [Lee et al., 2005], some cross-sectional studies did find associations with the prevalence of hearing impairment. We tried to account for this by including educational level in our analysis.

The strength of this study lies in the representativeness of our cohort as compared to the general population. At baseline there was a natural distribution of age and of all levels of hearing loss. Many earlier studies compared hearing impaired and normal hearing participants, while we studied the whole spectrum of hearing loss. Second, we structurally collected data and called in the help of a statistician for the analyses. Last, the prevalence of age-related hearing impairment was in line with prevalence numbers of other cohort studies using the WHO criteria [Agrawal et al., 2008; Lin et al., 2011; Mitchell et al., 2011].

CONCLUSIONS

In summary, in this study we showed that although hearing loss in the aging population was associated with type 2 diabetes, smoking, age and sex, we did not find an association with the progression of

hearing loss for any of these determinants. Worse baseline hearing levels were associated with a less rapid progression, which could be proof of a ceiling-effect in hearing deterioration.

This study indicates that the 4-year progression of hearing loss among older adults aged 66 - 87 is not influenced by the measured demographic and clinical determinants. To further clarify this more research with multiple follow up rounds is desired.

ACKNOWLEDGEMENTS

We would like to thank Tekla Enser for conducting all audiometry at our research center. This work was supported by a grant from the Heinsius Houbolt foundation and a grant from Cochlear.

ABBREVIATIONS

BMI = Body Mass Index; dB = decibel; DIN = digits-in-noise; kHz = kilo Hertz; MMSE = Mini-Mental State Examination; SRT = speech reception threshold.

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TABLES AND FIGURES

Table 1. Demographic characteristics of the study population at baseline.

Legend. Unless stated differently values are means and standard deviation for continuous variables or numbers and percentage for categorical variables. IQR = Inter quartile range, MMSE = Mini-Mental State Examination.

Figure 1. Average pure-tone thresholds of the study population at baseline.

Legend. Thresholds shown for three age categories. dBHL = decibels Hearing Level, Hz = Hertz.

Figure 2. Average hearing threshold at baseline and follow up.

Legend. Average pure-tone threshold for 0.5, 1, 2 and 4 kHz at baseline in relation to the average threshold at follow up shown for the three age categories. Every participant left of the line suffers decline of hearing during follow up. dBHL = decibels Hearing Level.

Table 2. Effect estimates from the final generalized estimating equation models for hearing acuity.

Legend. Reference group for each variable is female, finished higher education, no diabetes, never smoker, no alcohol consumption. * The SRT-analysis was also corrected for the high frequency hearing threshold. LOW = low frequencies threshold average (0.25, 0.50, and 1 kHz), SPEECH = speech frequencies threshold average (0.50, 1, 2, and 4 kHz), HIGH = high frequencies threshold average (2, 4, and 8 kHz), SRT = speech reception threshold, Edu = Educational level, MMSE = Mini-Mental State Examination, BMI = Body mass index, Syst. blood pr. = Systolic blood pressure, DM = Diabetes mellitus, Alc = Alcohol consumption.

Figure 3. Progression of high frequency hearing loss over time for different categories of participants.

Legend. All progression lines and 95% confidence intervals shown are for a participant with median outcomes (70 years, secondary educational level, MMSE score 28, BMI 27 kg/m², systolic blood pressure 149, average drinker, cholesterol ratio 3.63). Only sex, presence of diabetes and smoking status differed.

SUPPLEMENTARY MATERIAL

Table 1. Effect estimates from the generalized estimating equation full models for hearing acuity, including interaction terms.

Legend. Reference group for each variable is female, finished higher education, no diabetes, never smoker, no alcohol consumption. * The SRT-analysis was also corrected for the high frequency hearing threshold. LOW = low frequencies threshold average (0.25, 0.50, and 1 kHz); SPEECH = speech frequencies threshold average (0.50, 1, 2, and 4 kHz); HIGH = high frequencies threshold average (2, 4, and 8 kHz); SRT = speech reception threshold; Edu = Educational level; MMSE = Mini-Mental State Examination; BMI = Body mass index; Syst. blood pr. = Systolic blood pressure; Alc = Alcohol consumption.

Table 1. Demographic characteristics of the study population at baseline.

Characteristic	N = 650
Age, years	71.1 ± 4.1
Sex, female	338 (52.0%)
Education, primary	154 (23.7%)
secondary	344 (52.9%)
higher	152 (23.4%)
MMSE score (median, IQR)	28 (27;29)
Body Mass Index, kg/m ²	27.6 ± 3.7
Systolic blood pressure, mmHg	150 ± 20.6
Diabetes mellitus, yes	78 (12.0%)
Cholesterol ratio	3.74 ± 1.10
Smoking, never	217 (33.4%)
former	380 (58.4%)
current	53 (8.2%)
Alcohol, never	89 (13.7%)
light drinker	457 (70.3%)
above average	104 (16.0%)

Unless stated differently values are means and standard deviation for continuous variables or numbers and percentage for categorical variables. IQR = Inter quartile range, MMSE = Mini-Mental State Examination.

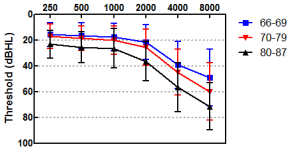
Table 2. Effect estimates from the final generalized estimating equation models for hearing acuity.

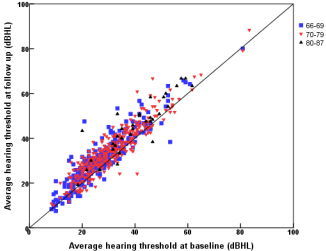
	LOW	<i>p</i>	SPEECH	<i>p</i>	HIGH	<i>p</i>	SRT*	<i>p</i>
Intercept	-25.08 [-46.23;-3.93]	0.020	-42.26 [-68.28;16.23]	0.001	-65.74 [-100.14;-31.34]	0.000	-11.73 [-17.01;-6.45]	0.000
Time (follow up years)	1.29 [0.86;1.72]	0.000	3.18 [2.80;3.55]	0.000	5.96 [5.46;6.46]	0.000	-2.93 [-3.23;-2.62]	0.000
Age (per year)	0.51 [0.32;0.70]	0.000	0.76 [0.53;0.98]	0.000	1.20 [0.92;1.48]	0.000	0.06 [0.00;0.11]	0.040
Sex	-2.04 [-3.60;-0.49]	0.010	2.18 [0.30;4.05]	0.023	7.53 [5.00;10.08]	0.000	-0.42 [-0.78;-0.06]	0.022
Edu: secondary	1.18 [-0.54;2.89]	0.179	1.79 [-0.28;3.85]	0.091	2.15 [-0.60;4.90]	0.126	0.00 [-0.41;0.40]	0.983
primary	1.81 [-0.36;3.98]	0.101	2.44 [-0.01;4.89]	0.051	2.86 [-0.40;6.13]	0.086	0.35 [-0.17;0.87]	0.183
MMSE	-0.05 [-0.50;0.41]	0.841	0.17 [-0.38;0.72]	0.537	0.34 [-0.42;1.10]	0.377	-0.07 [-0.17;0.04]	0.216
BMI (kg/m ²)	0.20 [-0.03;0.42]	0.083	0.11 [-0.15;0.37]	0.395	0.03 [-0.29;0.35]	0.850	0.02 [-0.04;0.07]	0.602
Syst. blood pr.	0.03 [-0.01;0.06]	0.141	0.03 [-0.01;0.07]	0.141	0.03 [-0.03;0.08]	0.362	0.00 [-0.01;0.01]	0.392
DM	2.47 [-0.10;5.04]	0.060	4.04 [0.97;7.12]	0.001	5.53 [1.83;9.23]	0.003	0.68 [0.04;1.31]	0.036
Cholestrol ratio	-0.31 [-1.01;0.39]	0.379	-0.07 [-0.89;0.76]	0.875	0.12 [-0.92;1.16]	0.822	-0.04 [-0.19;0.11]	0.603
Smoking: former	0.58 [-1.03;2.19]	0.478	0.58 [-1.36;2.53]	0.557	1.06 [-1.51;3.62]	0.420	-0.24 [-0.81;0.41]	0.233
current	3.45 [0.74;6.15]	0.012	3.35 [0.21;6.48]	0.036	4.96 [0.79;9.13]	0.002	-0.20 [-0.73;0.27]	0.523
Alc.: light drinker	-0.87 [-2.89;1.16]	0.400	-1.25 [-3.52;1.01]	0.278	-0.22 [-3.22;2.78]	0.888	-0.23 [-0.73;0.27]	0.371
above average	-0.78 [-3.41;1.85]	0.561	-0.84 [-3.79;2.11]	0.576	-0.77 [-4.68;3.13]	0.698	-0.31 [0.14;0.17]	0.333

Reference group for each variable is female, finished higher education, no diabetes, never smoker, no alcohol consumption. * The SRT-analysis was also corrected for the high frequency hearing threshold. LOW = low frequencies threshold average (0.25, 0.50, and 1 kHz), SPEECH = speech frequencies threshold average (0.50, 1, 2, and 4 kHz),

HIGH = high frequencies threshold average (2, 4, and 8 kHz), SRT = speech reception threshold, Edu = Educational level, MMSE = Mini-Mental State Examination, BMI = Body mass index, Syst. blood pr. = Systolic blood pressure, DM = Diabetes mellitus, Alc = Alcohol consumption

Frequency (Hz)





High frequency hearing threshold (dBHL)

Female

Male

1

2

1

2

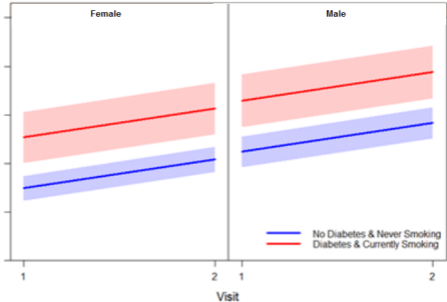
Visit



No Diabetes & Never Smoking



Diabetes & Currently Smoking



Supplementary material

Table 1. Effect estimates from the generalized estimating equation full models for hearing acuity, including interaction terms.

	LOW	<i>p</i>	SPEECH	<i>p</i>	HIGH	<i>p</i>	SRT*	<i>p</i>
Intercept	118.60 [-43.65;280.88]	0.152	97.64 [-89.72;284.99]	0.307	-57.15 [-308.43;194.14]	0.656	42.44 [0.06;4.36]	0.050
Time (follow up years)	4.54 [-5.03;14.10]	0.352	7.19 [-0.94;15.32]	0.083	4.34 [-5.95;14.64]	0.409	-2.18 [-8.71;4.36]	0.514
Age (years)	-3.46 [-7.85;0.94]	0.124	-3.12 [-8.18;1.95]	0.228	0.99 [-5.83;7.81]	0.777	-1.41 [-2.57;-0.25]	0.017
Age ² (years)	0.03 [-0.01;0.06]	0.078	0.03 [-0.01;0.06]	0.135	0.01 [-0.05;0.05]	0.951	0.01 [0.00;0.02]	0.014
Sex	-1.73 [-3.28;-0.18]	0.029	2.45 [0.63;4.27]	0.008	7.67 [-0.41;17.31]	0.000	-0.68 [-1.26;-0.10]	0.022
Edu: secondary	1.13 [-0.55;2.81]	0.187	1.71 [-0.28;3.68]	0.091	2.06 [-0.68;4.80]	0.140	0.08 [-0.48;0.64]	0.787
primary	1.93 [-0.23;4.10]	0.080	2.38 [-0.02;4.78]	0.052	2.62 [-0.74;5.98]	0.127	0.75 [-0.03;1.54]	0.060
MMSE	0.04 [-0.43;0.51]	0.864	0.24 [-0.29;0.77]	0.375	0.31 [-0.42;1.05]	0.406	-0.12 [-0.28;0.04]	0.130
BMI (kg/m ²)	0.17 [-0.04;0.38]	0.103	0.14 [-0.11;0.39]	0.260	0.08 [-0.25;0.40]	0.636	0.01 [-0.06;0.10]	0.738
Syst. blood pr.	0.02 [-0.01;0.05]	0.169	0.02 [-0.01;0.06]	0.167	0.02 [-0.03;0.07]	0.442	0.01 [-0.01;0.02]	0.074
Diabetes mellitus	1.83 [-0.80;4.45]	0.172	4.01 [1.02;7.01]	0.009	5.85 [2.17;9.53]	0.002	0.79 [-0.08;1.66]	0.074
Cholestrol ratio	-0.27 [-0.95;0.42]	0.444	-0.06 [-0.86;0.75]	0.891	-0.01 [-1.05;1.05]	0.998	-0.08 [-0.28;0.12]	0.429
Smoking: former	0.39 [-1.20;1.97]	0.634	0.44 [-1.43;2.31]	0.643	1.25 [-1.29;3.79]	0.336	0.02 [-0.60;0.63]	0.961
current	2.08 [0.16;5.45]	0.038	2.09 [-0.07;5.87]	0.056	5.47 [1.36;9.57]	0.009	0.05 [-0.89;0.98]	0.924
Alc.: light drinker	-0.57 [-2.64;1.49]	0.587	-1.28 [-3.52;0.96]	0.262	-0.59 [-3.70;2.53]	0.712	-0.37 [-1.20;0.46]	0.384
above average	-0.36 [-3.01;2.29]	0.790	-0.68 [-3.58;2.23]	0.647	-1.01 [-5.08;3.07]	0.628	-0.27 [-1.27;0.73]	0.599
Time x sex	-0.47 [-1.44;0.50]	0.342	-0.37 [-1.25;0.51]	0.406	-0.24 [-1.42;0.93]	0.687	0.34 [-0.31;1.00]	0.303

Time x MMSE	-0.18 [-0.46;0.10]	0.208	-0.13 [-0.38;0.12]	0.296	0.06 [-0.26;0.38]	0.711	0.04 [-0.15;0.23]	0.685
Time x BMI	0.06 [-0.08;0.19]	0.406	-0.05 [-0.17;0.06]	0.370	-0.09 [-0.24;0.05]	0.201	0.00 [-0.09;0.09]	0.973
Time x syst. blood pr.	0.01 [-0.01;0.03]	0.539	0.01 [-0.01;0.03]	0.380	0.01 [-0.02;0.03]	0.487	-0.02 [-0.03;0.00]	0.026
Time x diabetes mellitus	1.14 [-0.41;2.69]	0.150	-0.04 [-1.21;1.13]	0.941	-0.63 [-2.13;0.86]	0.408	-0.36 [-1.50;0.77]	0.532
Time x cholesterol ratio	-0.06 [-0.42;0.30]	0.746	0.01 [-0.33;0.34]	0.977	0.24 [-0.28;0.76]	0.358	0.07 [-0.18;0.32]	0.571
Time x secondary education	0.01 [-1.06;1.07]	0.994	0.07 [-0.84;0.98]	0.886	0.15 [-1.01;1.31]	0.801	-0.08 [-0.76;0.60]	0.818
Time x primary education	-0.57 [-1.97;0.84]	0.427	-0.19 [-1.36;0.98]	0.751	0.48 [-1.01;1.97]	0.526	-0.73 [-1.64;0.17]	0.112
Time x former smoker	0.28 [-0.79;1.36]	0.608	0.15 [-0.75;1.05]	0.743	-0.42 [-1.56;0.73]	0.475	-0.31 [-1.00;0.37]	0.370
Time x current smoker	1.03 [-0.57;2.63]	0.205	0.65 [-0.92;2.21]	0.417	-1.02 [-2.91;0.86]	0.287	-0.51 [-1.54;0.51]	0.325
Time x light drinker	-0.58 [-2.10;0.94]	0.456	0.07 [-1.12;1.27]	0.903	0.75 [-0.77;2.28]	0.335	0.37 [-0.52;1.27]	0.411
Time x above average	-1.05 [-2.80;0.70]	0.238	-0.55 [-1.98;0.89]	0.453	0.44 [-1.41;2.29]	0.643	0.10 [-1.00;1.20]	0.855

Reference group for each variable is female, finished higher education, no diabetes, never smoker, no alcohol consumption. * The SRT-analysis was also corrected for the high frequency hearing threshold. LOW = low frequencies threshold average (0.25, 0.50, and 1 kHz); SPEECH = speech frequencies threshold average (0.50, 1, 2, and 4 kHz); HIGH = high frequencies threshold average (2, 4, and 8 kHz); SRT = speech reception threshold; Edu = Educational level; MMSE = Mini-Mental State Examination; BMI = Body mass index; Syst. blood pr. = Systolic blood pressure; Alc = Alcohol consumption.