Research Article

The Role of Genetic Factors for Hearing Deterioration Across 20 Years: A Twin Study

Renata Bogo,1 Ahmed Farah,2 Ann-Christin Johnson,1 Kjell K. Karlsson,3 Nancy L. Pedersen,4 Magnus Svartengren5 and Åsa Skjönsberg1,3

1Department of Clinical Science, Intervention and Technology, Section of Audiology, Karolinska Institutet, Huddinge, Sweden. 2Public Health Agency of Sweden, Stockholm, Sweden. 3Department of Audiology and Neurotology, Karolinska University Hospital, Huddinge, Sweden. 4Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. 5Department of Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden.

Address correspondence to Åsa Skjönsberg, PhD, Alfred Nobels Allé 10, SE-141 83 Huddinge, Sweden. Email: asa.skjonsberg@ki.se

Abstract

Background. Hearing deterioration at advanced ages is associated with environmental exposures (e.g., to noise and solvents) and genetic influences may also be important. Little is known about the role of genetic influences on hearing when evaluated longitudinally. We sought to investigate longitudinal hearing loss in a cohort of adult male twins to evaluate the importance of genetic and environmental factors for hearing deterioration over time.

Methods. Hearing using conventional clinical audiometry was assessed in 583 male twins (128 monozygotic twin pairs and 111 dizygotic twin pairs) aged 34–79 at baseline and again two decades later. The hearing thresholds at two time points were compared at each frequency and in two different frequency regions. Genetic analyses were based on structural equation models. Bivariate Cholesky decomposition was used for longitudinal analysis.

Results. The prevalence of hearing loss increased over time in better and worse ear. The hearing threshold shift was more pronounced in the high-frequency region, especially at 8000 Hz. Genetic influences were moderate (heritability: 53%–65%) for pure-tone averages at both lower and higher frequencies, and were of equal magnitude at baseline and follow-up. In contrast, environmental influences were of substantial importance (55%–88%) for rate of change of the hearing threshold over the 18-year period.

Conclusions. Genetic factors are of considerable importance for level of hearing acuity, but environmental factors are more important for rate of change over an 18-year period.

Key Words: Aging—Genetic—Hearing loss—Pure-tone average—Threshold shift—Twins.

Decision Editor: Stephen Kritchevsky, PhD

Approximately, 5% of the population worldwide is affected by hearing loss to some degree, whereas 30% of persons 65 years and older have hearing loss (1). Age-related hearing loss has been considered as a part of the normal aging process (2) and is one of the most common social and health problems (3,4). It is a complex disorder, which is influenced by many different factors such as exposure to noise, lifestyle, individual life events, and genetic factors (5). The characteristic audiogram in age-related hearing loss is a gradually sloping curve, which indicates hearing loss in the high-frequency range starting from 2000 Hz (6).

Genetic and environmental factors contribute to age-related hearing loss as has been shown in animal models (7,8) and human studies (9). Twin and family studies, which compare similarity in monozygotic (MZ) and dizygotic (DZ) twin pairs or family members, are important...
tools to evaluate the relative importance of genetic and environmental factors for variation in a trait (heritability). Twin studies have shown that genetic factors may account for 40%–70% of the variation in hearing loss (10–14), whereas a family study reports heritability estimates from 35% to 55% (15). A Finnish twin study of women (10) found that heritability is constant at about 60% through all frequencies, whereas a Swedish twin study of males aged 65 and older (11) reports a heritability of 47% for high frequencies (3000–8000 Hz). Similarly, Wingfield and colleagues (12) found that genetic contributions range from 50%–76% in middle- and high-frequency ranges, and better ear (BE) or worse ear (WE). Garringer and colleagues (13) report a heritability of 61% for hearing loss, and linkage results that implicate genetic variation in the DFNA18 region of chromosome 3q. Finally, the heritability of self-reported hearing loss was 40% in Danish twins (14). Nevertheless, none of these studies have evaluated the impact of genetic factors on hearing loss in a longitudinal setting.

The aims of this study were to explore how aging contributes to hearing loss in an older male twin cohort assessed longitudinally and to investigate how genetic factors influence longitudinal change in hearing thresholds over time in two different frequency regions potentially differentially affected by the aging process.

Materials and Methods

Participants

The study population is a twin cohort of 1,624 Swedish male twins from Stockholm and Uppsala Counties, born between 1914 and 1958 (11). Both members of 557 male twin pairs (1,114 individuals) provided audiometric data collected between 1991 and 1994 and form the basis for a follow-up approximately 18 years later (2010–2013). From the baseline sample, 219 individuals were lost due to death between the two time points, resulting in 895 possible participants for follow-up. A total of 583 individuals (65%) participated in the assessments in 2010–2013. Reasons for not participating were death after the start of the measurements (n = 31), refusal (n = 160) or unable to participate (n = 53), and no response (n = 68).

Zygosity was determined based on comparisons of 47 single nucleotide polymorphism (SNPs) markers distributed across the genome (16). If DNA was unavailable, zygosity was based on questions regarding similarity, a method that has over 98% accuracy (17). At follow-up, 256 MZ twins, 222 DZ twins, and 105 singletons (ie, only one member of the pair) participated. For genetic analyses, only complete pairs were included (128 MZ and 111 DZ pairs).

The project was reviewed by and has received approval from the regional ethical review board in Stockholm, Sweden (2009/378-31 and Huddinge Hospital [18/92]).

Hearing Assessment

Pure-tone audiometry was performed using the ascending method (18), in a soundproof booth. Air conduction thresholds between 125 and 8000 Hz were measured for each ear separately. Clinical audiometers with TDH39 headphones were used. The safety limit due to national regulations was considered. If individual hearing thresholds exceeded the maximum output limit, the unachieved hearing thresholds were registered as 99 at 125 Hz, as 109 at 250 Hz, or as 129 for the remaining frequencies (11).

Pure-Tone Audiometry Averages

Pure-tone averages (PTA) of the four frequencies 500, 1000, 2000, and 4000 Hz (PTA4) as well as at four higher frequencies (3000, 4000, 6000, and 8000 Hz [HPTA4]) were calculated at both time points. PTA4 was included to reflect World Health Organization definitions (19), whereas HPTA4 is intended to mirror the high frequencies that are more affected by aging (6,20).

The HPTA4 thresholds at baseline for the left and the right ears were compared to assign the BE and the WE. The PTA4 assignment of BE and WE was based on the HPTA4 calculations to maximize the potential to discriminate between a BE and WE.

The longitudinal change of hearing using these averages was calculated as the difference between the baseline and follow-up measurements and is called threshold shift. Threshold shifts are also calculated for individual frequencies.

Hearing deterioration was also calculated as the decline in decibels per year for both averages (PTA4 and HPTA4) as well as for each individual frequency.

To evaluate the prevalence of hearing loss in this cohort, the value more than 25 dB was used for both PTA4 and HPTA4.

Figure 1. Path diagram of the bivariate longitudinal model of additive genetic (A), shared (C), and individual-specific environmental (E) components of variance at baseline and follow-up. MZ = monozygotic twin pairs; DZ = dizygotic twin pairs.
Statistical Analysis

The mean age for all participants at follow-up was 66.6. In order to divide the sample at the mean and have both members of the twin pair in the same age group, the cutoff was adjusted to 66.4. For further analysis, the younger group had 288 participants and the older group had 295 participants.

PTA4 and HPTA4 were not normally distributed. Therefore, both PTA4 and HPTA4 were transformed as log(PTA4 + 10) and log(HPTA4 + 10) for subsequent genetic analyses.

Stata 11.2 (Stata Corp LP, College Station, TX) was used to compare the hearing thresholds between the younger and older groups. Fisher’s Exact and McNemar’s Test of association for categorical variables were used to compare prevalence of hearing loss at baseline versus follow-up.

Genetic modeling draws on the fact that MZ twins share 100% of their genes, whereas DZ twins share approximately half of their segregating genes. Both MZ and DZ twins are assumed to share family environment, and thus, a greater similarity in MZ pairs than DZ pairs gives an indication of the importance of a genetic component.

We used a classical structural equation model adjusted for age to decompose the total phenotypic variation into additive genetic (A), nonadditive (dominance) genetic (D), shared environmental (C), and individual-specific environmental variance (E). It is not possible to simultaneously calculate C and D with only MZ and DZ twins, thus, both ACE and ADE models were tested. For the yearly deterioration of the hearing threshold, we used a univariate model, whereas a Cholesky decomposition as depicted by the path diagram shown in Figure 1 (21) was used to estimate the importance of these latent factors for baseline and follow-up assessments. The first latent factors load on both time point 1 (1991–1994) and time point 2 (2010–2013), whereas the second latent factors load on time point 2.

Heritability, the proportion of the total variance attributable to the additive genetic variance in the univariate model is computed by the ratio \( a^2 / (a^2 + c^2 + e^2) \). In the bivariate case, heritability is obtained as the ratio \( a^2_{11} / (a^2_{11} + c^2_{11} + e^2_{11}) \) at baseline and at follow-up as \( a^2_{21} + a^2_{12} / (a^2_{21} + a^2_{12} + c^2_{21} + c^2_{12} + e^2_{21} + e^2_{12}) \). The relative contributions of shared and individual-specific environments are obtained by replacing the numerators of these ratios to corresponding squared path coefficients of shared and unique environment, respectively.

A series of nested models were run to test the extent to which each of the components were significant. Each component was

Figure 2. Mean hearing thresholds for all participants (n = 583; Panel A), monozygotic twins (n = 289), and dizygotic twins (n = 294; Panel B) at baseline (hollow triangle and hollow circle) and at follow-up (filled triangle and circle).
Results

Age at baseline was 48, 47, and 52 for MZs, DZs, and singletons, respectively, whereas age at follow-up was 66, 66, and 70. The mean follow-up time was 18.5, 18.5, and 18.2 for the three groups. Singletons differed significantly \((p < .05)\) from MZs and DZs on age at baseline, at follow-up, and follow-up time. Older age at baseline was the most important factor for not participating at follow-up (odds ratio due to age = 1.03). The group that did not participate at follow-up also had a more pronounced hearing impairment at baseline (odds ratio from 1.01 to 1.02 dependent on ear and frequency range).

Hearing Deterioration and Prevalence of Hearing Loss

Mean hearing thresholds are depicted in Figure 2 (Panel A) and by zygosity in Panel B. Already at baseline measurement, the mean audiogram showed a sloping curve in the high-frequency range. There were no significant differences between MZs and DZs at baseline or follow-up.

The longitudinal hearing deterioration (threshold shift) across approximately 18 years for all frequencies, PTA4 and HPTA4 as well as deterioration in decibel per year are reported in Table 1. The 8000 Hz showed the greatest threshold shift. Hearing deterioration in the older age group extends to lower frequencies compared with the younger age group. The older participants had significantly greater hearing loss in both the BE and the WE compared with the younger participants at all frequencies, as well as in PTA4 and in HPTA4. HPTA4 showed greater threshold shifts across the 18-year-follow-up than PTA4.

Rate of deterioration in decibels per year was more pronounced at and above 2000 Hz. The older group differed from the younger group already at 500 Hz and even more so at high frequencies, with a maximum loss at 8000 Hz (Table 1). Overall, the WE showed significantly greater deterioration per year than the BE at all frequencies, PTA4 and HPTA4.

The prevalence of hearing loss (>25 dB hearing level) differed significantly between age groups, ears, PTA4 and HPTA4, and time points (Table 2). Already at baseline, the prevalence of hearing loss based on HPTA4 was at least twice as high as for PTA4, regardless of the comparison. An eighth of the younger group and nearly half of the older group had a BE hearing loss (HPTA4 >25 dB) at baseline. Eighteen years later, the prevalence of hearing loss had increased nearly fivefold for the younger group, and almost all individuals in the older group had a hearing loss at the high-frequency region.

Genetic Analyses

The means and variances of the transformed hearing thresholds did not differ by zygosity or by classification of twins as twin 1 or twin 2. Thus, the basic assumptions of the twin method were met.

MZ pairs were consistently more similar than DZ pairs (Table 3), suggesting that genetic factors are of importance for hearing loss.

![Table 1. Hearing Deterioration as Threshold Shifts (dB) and Decibels per Year for All Frequencies From 125 to 8000 Hz for the Better and the Worse Ear](https://academic.oup.com/biomedgerontology/article-abstract/70/5/647/647598)

![Table 2. Genetic Analyses](https://academic.oup.com/biomedgerontology/article-abstract/70/5/647/647598)
Table 2. Prevalence of Hearing Loss (defined as PTA4 or HPTA4 > 25 dB) by Age Group

<table>
<thead>
<tr>
<th></th>
<th>Younger (n = 288)</th>
<th>Older (n = 295)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, %</td>
<td>Follow-Up, %</td>
</tr>
<tr>
<td>PTA4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Worse</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>HPTA4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>13</td>
<td>61</td>
</tr>
<tr>
<td>Worse</td>
<td>26</td>
<td>69</td>
</tr>
</tbody>
</table>

Notes: HPTA4 = pure-tone average of the four frequencies 3000, 4000, 6000, and 8000 Hz; PTA4 = pure-tone average of the four frequencies 500, 1000, 2000, and 4000 Hz.

at baseline as well as follow-up. For all measures except baseline PTA4 in the BE, the MZ intraclass correlations were more than twice the size of DZ pairs, suggesting nonadditive genetic effects. Subsequent model fitting analyses (Supplementary Table S1) indicated that the best fitting model was the parsimonious AE model. There were essentially no differences in the magnitude of the genetic effect between baseline and follow-up (Table 3), and individual-specific environmental influences (E) consistently accounted for approximately 40% of the variance. The same genetic influences of importance at baseline were also of importance at follow-up; no new genetic components came into play at follow-up (i.e., $a_{22}$ was not significant).

Change in hearing thresholds in decibel per year showed lower values for A but much higher values for E (Table 4), indicating that individual-specific environments are more important for the rate of change in the hearing threshold than for the level at either baseline or follow-up. Environmental influences appear to be greater for rate of decline in the BE than the WE.

Discussion

In this longitudinal twin study, we characterized hearing impairment and rates of deterioration across 18 years. Genetic factors are of considerable importance for level of hearing impairment at baseline and at follow-up (heritability: 53%–65%), but environmental factors are more important for rate of loss over an 18-year period, particularly for the BE. These longitudinal findings confirm the results of previous cross-sectional studies (10–13) and provide new evidence regarding influences on levels versus rate of change.

Two important findings became apparent from the longitudinal analyses; first, analyses of rate of loss (in decibels per year) showed that environmental factors were more prominent for the BE. Thus, although there is no difference between the BE and WE in the impact of environmental stressors at any one occasion in adulthood, rates of change in the BE appear to reflect these stressors. These findings complement those of Wingfield and colleagues (12), who also found no differences in environmental impact between BE and WE at one occasion, and point to the importance of examining change across time. Environmental variance at any one time point does not need to be the same as the relative importance of environmental variance for rates of change (deterioration). Our findings suggest that environmental exposures are more important than genetic influences for the rate of hearing deterioration, but at follow-up, the relative importance of genetic influences is greater.
Table 4. Intraclass Correlations and Estimated Genetic (A) and Individual-specific Environmental (E) Proportions of Variance for Change of Hearing Threshold in decibel per Year, Adjusted for Age

<table>
<thead>
<tr>
<th></th>
<th>Intraclass Correlation</th>
<th>Proportion of Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ Twin Pairs (n = 128)</td>
<td>DZ Twin Pairs (n = 111)</td>
</tr>
<tr>
<td>PTA4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better ear</td>
<td>0.17</td>
<td>0.00</td>
</tr>
<tr>
<td>Worse ear</td>
<td>0.51</td>
<td>0.19</td>
</tr>
<tr>
<td>HPTA4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better ear</td>
<td>0.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Worse ear</td>
<td>0.39</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Notes: A = genetic proportion of variance; DZ = dizygotic twin pairs; E = individual-specific environment proportion of variance; HPTA4 = pure-tone average of the four frequencies 500, 1000, 2000, and 4000 Hz; MZ = monozygotic twin pairs; PTA4 = pure-tone average of the four frequencies 3000, 4000, 6000, and 8000 Hz. 95% Confidence intervals are within the brackets.

Examples of relevant exposures that may influence age-related deterioration include external factors as exposures to noise, solvent, drugs, and other auditory stress factors, both at work and at leisure time (23,24). Or, conversely, it may be that further age-related change in the WE indeed depends to a greater extent on genetic susceptibility. Genetic factors underlie several ear diseases such as otosclerosis (25), otitis media (with or without effusion) (26,27), and Meniere’s disease (28), which often affects hearing only in one ear and may eventually affect the other ear a few years later. The cohort in this study was unscreened for these diseases.

The second interesting finding from the longitudinal analyses is the relative stability of the importance of genetic influences on hearing acuity. The same genetic influences of importance in midlife are important nearly 20 years later. In other words, there appears to be no new genetic influences coming into play later in life.

The annual rates of decline in hearing ability (decibels per year) were very similar for PTA4 in both the BE and the WE (0.5 vs 0.8 decibels per year) for both younger and older participants, showed a steeper decline in the higher frequency and especially at 8000 Hz as could be expected, and were more pronounced in the BE in accordance with other longitudinal studies (29–32). The older participants showed the most marked hearing deterioration, consistent with the ISO 7029 (33) but more pronounced than a recent analysis of the predictors of hearing acuity (32).

Although only a fraction of the younger group had a hearing loss that exceeded 25 dB at PTA4, however, a quarter of this age group met the threshold for hearing loss in the HPTA4 region at baseline and more than half at follow-up. These results indicate the importance of high-frequency monitoring in the general population, which can lead to earlier (midlife) recognition and rehabilitation of hearing impairment (12,32,34). Age-related hearing loss is a very slow process, and by the time patients or their relatives become aware of it, the problem is most often more pronounced than they believe themselves. By screening middle-aged persons on a regular basis and taking the high-frequency region into account during referral to rehabilitation, we believe that patients will be more familiar and more comfortable with training to use their hearing aids in everyday life. An understanding of the relatively strong genetic impact on hearing acuity together with knowledge of environmental exposures could serve as a tool for targeting the rehabilitation of hearing loss, for example, in directed hearing screening programs and the initiation of earlier hearing-aid fitting to individuals more susceptible to developing hearing loss (34).

This study has both strengths and limitations. To our knowledge, this is the only twin study with almost 20-years follow-up, providing unique information about changes not only in thresholds but also in genetic and environmental influences for hearing loss across time. The audiometric threshold measurements at 10 frequencies were performed by a skilled audiologist using clinical standards regarding methods and soundproof measuring booth. Nevertheless, there were a small number of unachieved hearing thresholds; the higher the frequency, the greater the number, and the highest number was at 6000 Hz (n = 13). Limitations include restriction to an only male cohort in an urban area and greater dropout at follow-up in older participants. Half of the individuals who refused to participate were gainfully employed; their reason for refusal was lack of time due to workload. Causes of dropout would result in an underestimation of the magnitude of longitudinal changes; however, this would have no importance of the variation of estimation of genetic and environmental factors. Finally, as with all twin studies, we have little power to estimate C. For most phenotypes, there is little evidence of C in mid or late life.

In conclusion, the prevalence of hearing loss increases with age. Genetic influences are substantial for hearing loss both in midlife and after 18 years of follow-up, but environmental factors are more important for rate of change over an 18-year period.

Supplementary Material
Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

Funding
This study was funded by grants from Swedish Council for Working Life and Social Research (FAS) (2008-1054) and was part of the Hearing Disabilities in Working Life and Society (2006-1526).

Acknowledgments
We thank Eva B. Svensson and Satu Turunen-Taheri at the Unit of Audiology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet for help with the data collection.

Conflict of Interest
None declared.
References


Downloaded from https://academic.oup.com/biomedgerontology/article-abstract/70/5/647/647598 on 30 May 2018