Multivariate statistics: Assignment 1

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Abstract

1 Introduction and data exploration

This report assesses hearing thresholds for a sample of 546 healthy male volunteers. The subjects were 52 years old on average at the start of the study and are followed for an average of 7.57 years. The hearing threshold is measured, on average, every 1.59 years. Table 1 describes the demographics in more detail. It can be seen that the data is highly unbalanced; there is a lot of variation in the time a volunteer is followed and in the number of times a volunteer's hearing threshold is measured. Normally, each ear is measured at each visit but this only happened in 93.22% of all visits. The left (right) ear was tested in 96.72% (96.5%) of all visits.

Previous research on the hearing data of males in the Baltimore Longitudinal Study of Aging (BLSA) showed a change in hearing threshold for all age groups but especially the older population (Brant and Fozard 1990). In contrast to our dataset, Pearson et al. (1995) and Morrell et al. (1997) consider females in their study. They similarly found a decrease in hearing sensitivity for all ages at 500Hz and included a quadratic function of age to predict the hearing threshold, as in Verbeke, Spiessens, and Lesaffre (2001). Additionally, a statistically significant learning effect from the first visit to subsequent visits was found (Morrell et al. 1997; Verbeke, Spiessens, and Lesaffre 2001). Morrell et al. (1997) observed that hearing levels are slightly poorer on average on the left compared to the right ear and that the variance in the hearing threshold is higher for people with a higher age.

Figure 1 shows the trends in the hearing threshold for all volunteers over time. These figures shows that many volunteers' hearing threshold over time have an erratic pattern meaning there is likely high variability **within subjects**. Additionally, variability **between subjects** is also high, especially for older volunteers.

1.1 Mean, variance and correlation structure

Figure 2 shows the mean and 95% confidence interval for the hearing threshold (dB) for different age groups. The thresholds for the age groups are chosen such that each group is approximately the same size (between 141 and 149 measurements in each group). The graph shows that the variance increases with age and there doesn't seem to be a significant difference, on average, between left and right ears.

Figure 3 shows Loess smoothing curves by age category and side of the ear. The trend in the average is slightly increasing for most groups. For the oldest group, there is a more pronounced
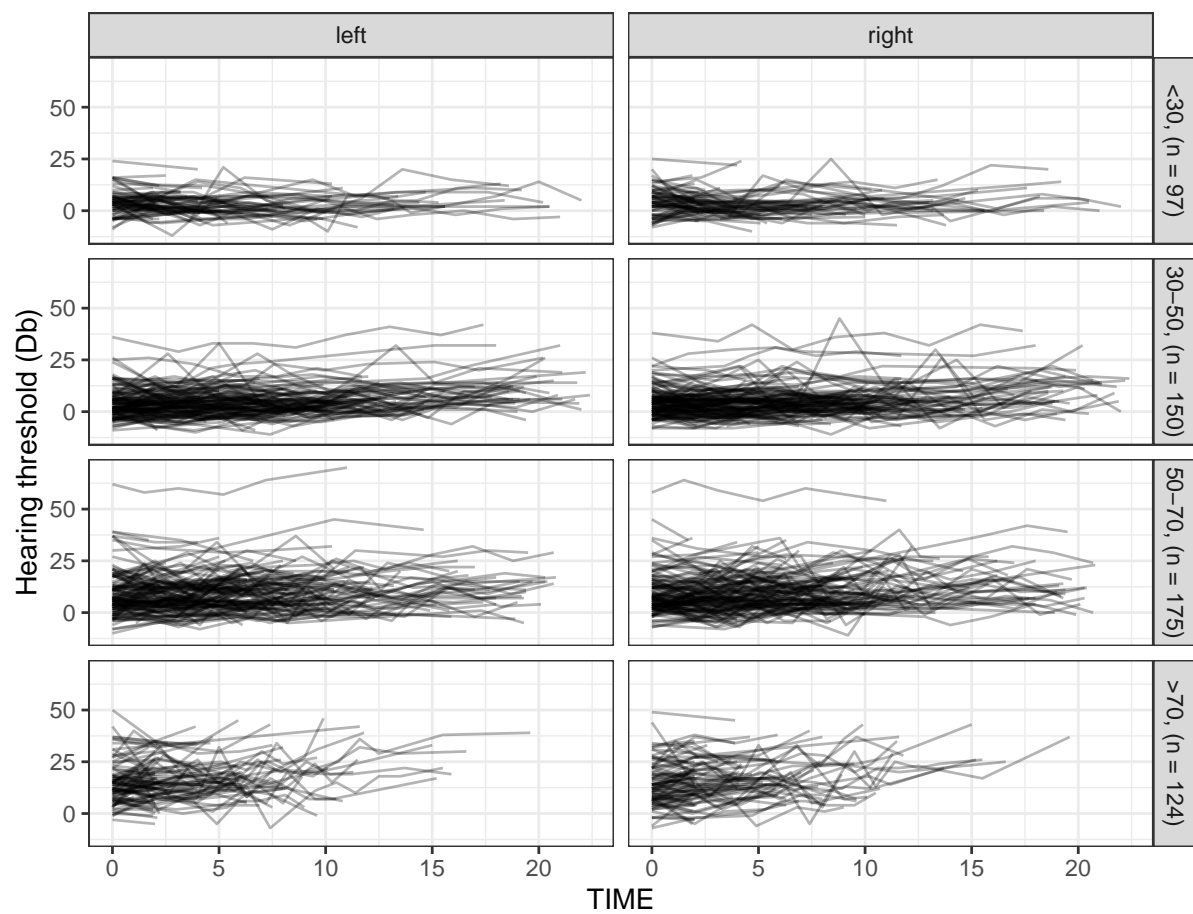
Figure 1: Hearing threshold over time, divided by left and right ear and by age group at the start of the study

increase in the hearing threshold. Additionally, the estimated standard errors around the mean are larger as time increases, likely due to dropout. Based on the estimated averages from 3, squared residuals can be calculated. Figure 4 shows the Loess smoothed variance function for each group. Overall, the variance seems quite constant over time and it is higher for older subjects. The downward trend at time > 15 for the oldest age group can possibly not be trusted due to limited data.

The data has a hierarchical (grouped) structure since each individual (id) is measured several times over the years. Some basic descriptive statistics were derived using the *statsBy* function from the psych package. The intraclass correlation (percentage of variance due to groups) is 0.69 for the hearing threshold (y) and, as expected, very high (0.93) for age at the time of measurement.

The total correlation between y and the age at the measurement, ignoring the hierarchical structure, is 0.45. Following Marzban et al. (2013) and Mongomery (2017), the correlation matrix for each subject that has at least 2 measurements for both ears is calculated, one can obtain within-group correlations and variances. Figure 5 shows the histograms over all individuals for the correlation between the age at the measurement and y, and the variances for both age and y (though the variance in age is not very informative). The mean or median of all within-group correlations is often used as a measure of within-group correlation. The mean (0.15) and median (0.23) of the within-group correlations are indicated in red and blue respectively on the graph. It can be seen that within-group correlation spans the entire range from -1 to 1, meaning that age has a strong positive relationship to the hearing threshold for some and a strong negative relationship for others. Age will be a good predictor for hearing threshold for some but not

Table 1: Demographics for all respondents

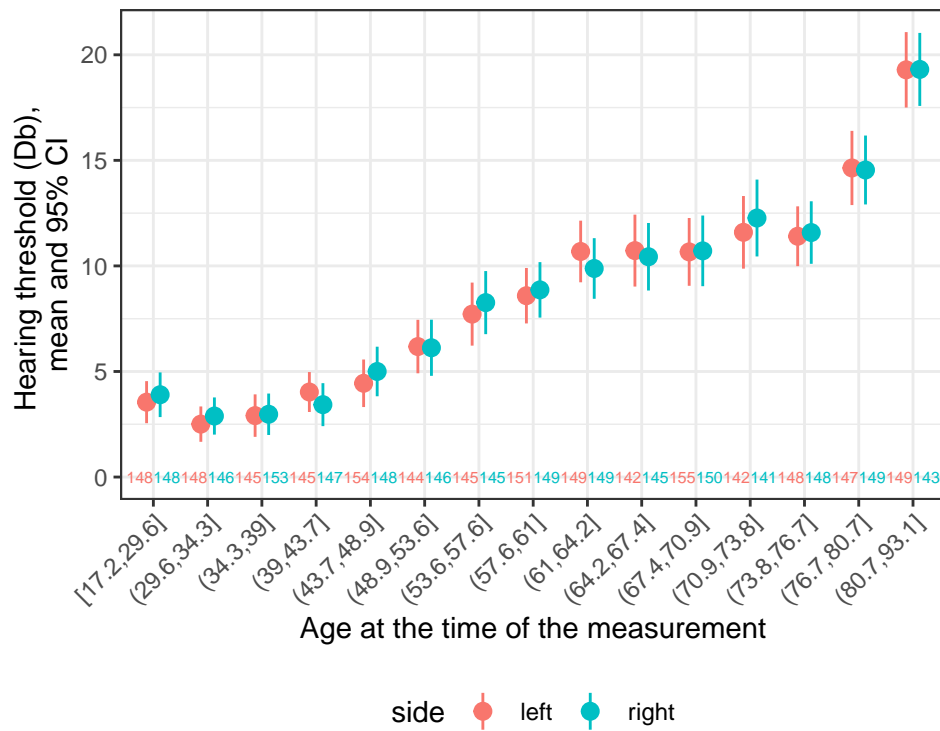| **Age at the beginning of the study**	
min	17.20
max	87.00
median	54.10
mean (sd)	51.99 ± 18.70
Years of follow-up	
min	0.00
max	22.40
median	6.30
mean (sd)	7.57 ± 6.30
Number of visits	
min	1
max	15
median	3.00
mean (sd)	4.19 ± 2.88

Figure 2: Hearing threshold over time, divided by left and right ear. The numbers in the bottom show the number of measurements that were taken.

for others. Between-group correlation is obtained by averaging the age at measurement and the hearing threshold for each group (see scatterplot in Figure 5) and then computing the correlation across the groups, obtaining 0.54.

Panel B in Figure 5 shows that the correlation between the side of the ear that is measured and the hearing threshold (y) is high for some but small for most individuals. Panel C in Figure 5 shows that the variance in the hearing threshold is usually less then 50 but can be very large for some individuals.
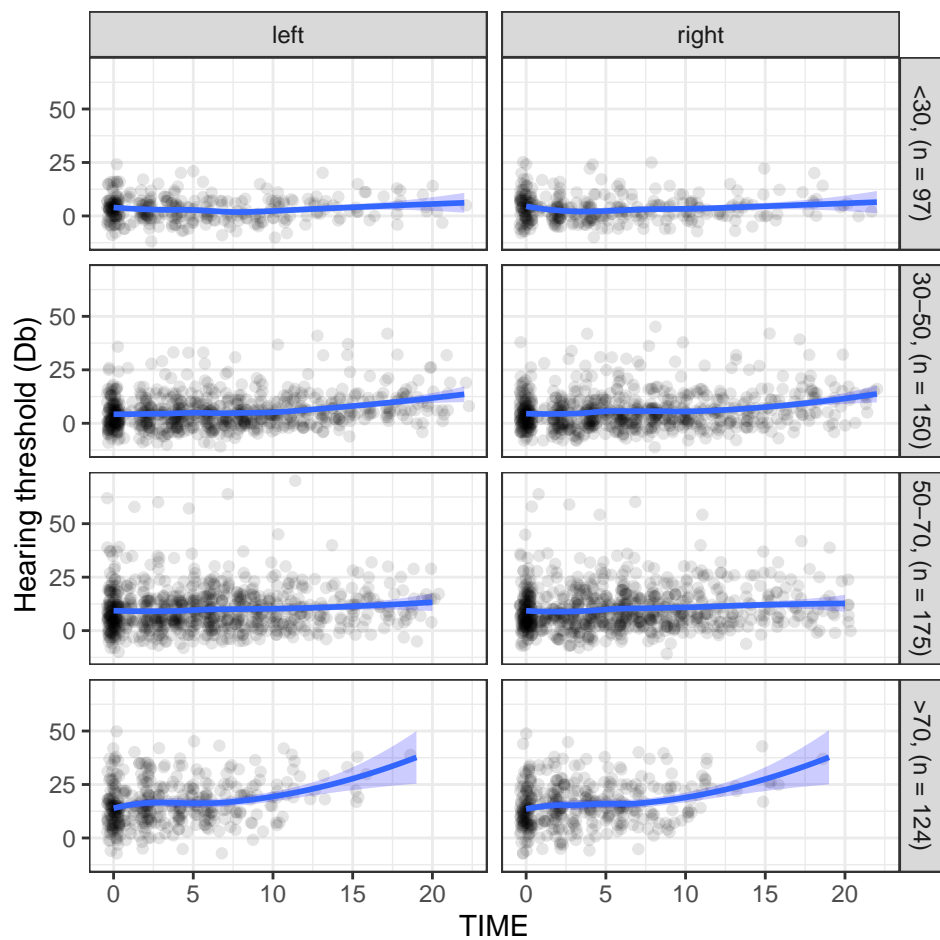
Figure 3: Loess smoothing on the hearing threshold since start of the study, divided by left and right ear and age group at the start of the study.
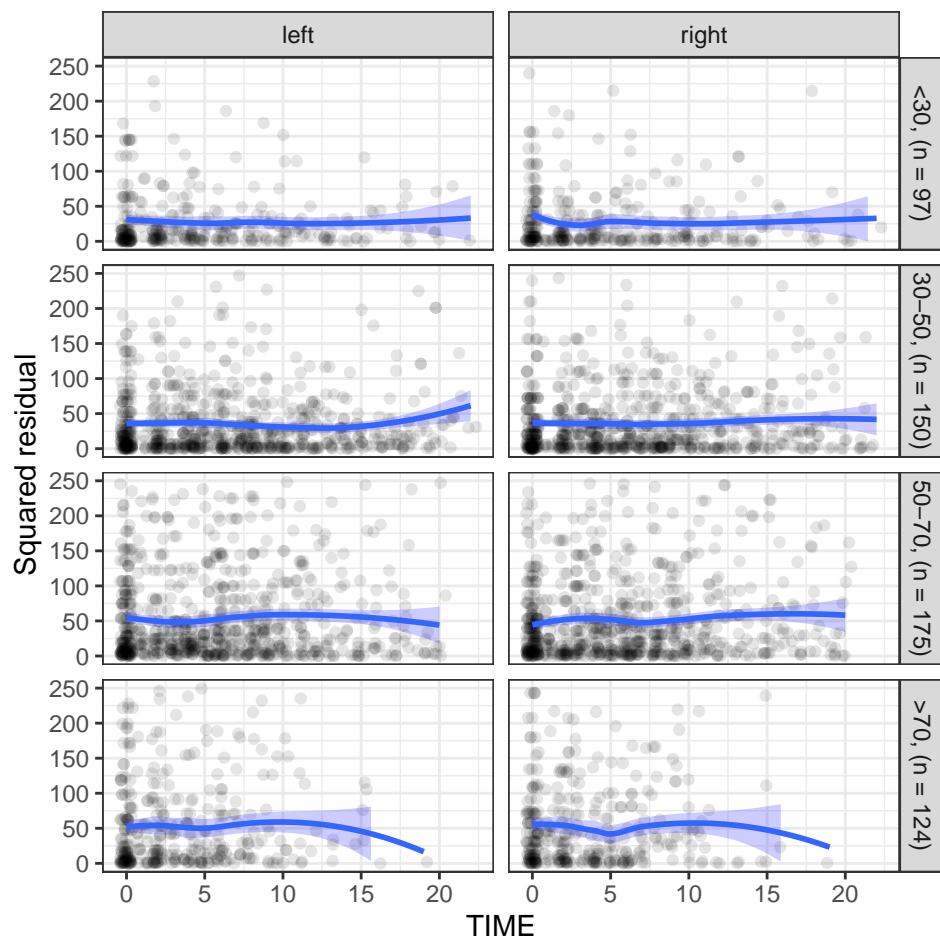
Figure 4: Loess smoothed variance in the hearing threshold since start of the study, divided by left and right ear and age group at the start of the study.
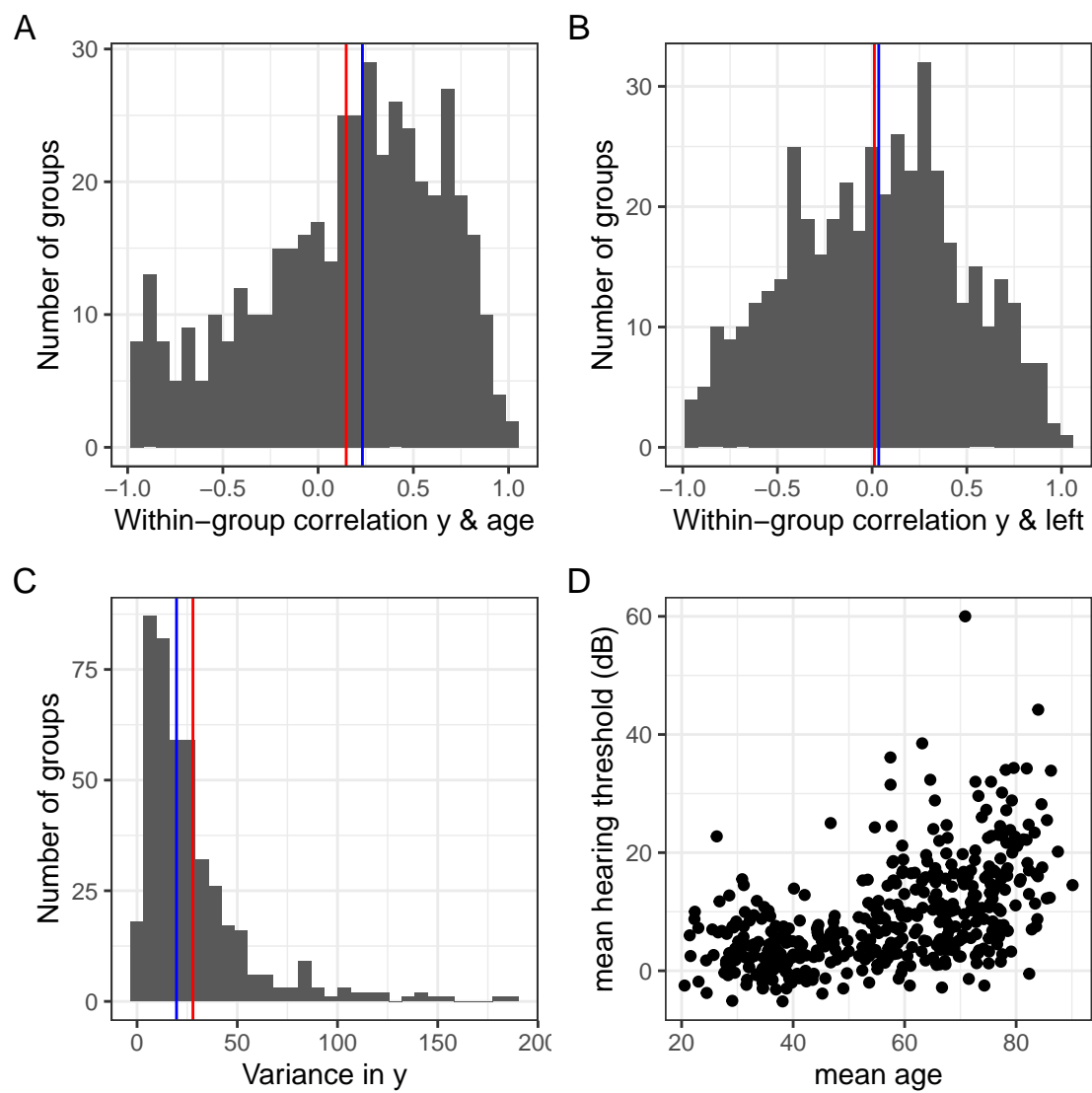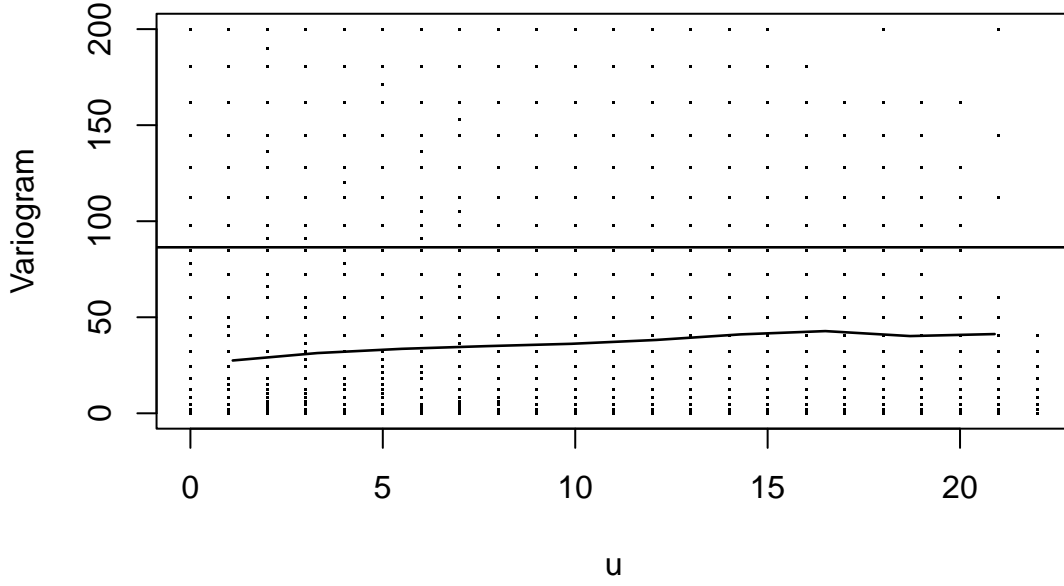
Figure 5: The mean is indicated in red, the median in blue

Lastly, a semi-variogram is constructed using the *joineR* package. The total variance is estimated to be 86.42. Measurement error is approximately 22.29, the serial correlation component is approximately 19.18 and the between-subject variability is thus 44.95.

2 Methodology

In this section, we explore a couple of different methods to analyze the data. All analysis was carried out with the statistical software R. All scripts are freely available at this git repository.

2.1 Summary statistics

One possibility to deal with the hierarchical structure of the data is to summarize the data and reduce the number of measurements per subject to one.

A simple paired-t test can check whether there is a significant difference between the left and right ear. For this test, the difference $\Delta_i^1 t$ is calculated between the hearing threshold of the left and right ear for each subject i and at each time instance t that both ears were measured (equation (1)).

$$\Delta_{it}^1 = Y_{ilt} - Y_{irt} \tag{1}$$

If the focus is on the change in hearing threshold over time, we can, for instance, calculate the average change in the hearing threshold for each subject i, Δ_i^2 as in equation (2) where Y_{ijk} is the kth measurement for ear $j \in \{l, r\}$ of subject i and n_{ij} is the total number of measurements of ear j of subject i.

$$\Delta_i^2 = \frac{(Y_{iln_{il}} - Y_{il1}) + (Y_{irn_{ir}} - Y_{ir1})}{2} \tag{2}$$

Alternatively, if the difference between the left and right ear is an important effect to analyse, equation (3) shows an alternative with one summary measure for each ear j of subject i with at least two measurements over time. n_{ij} is the total number of measurements of ear j of subject i.

$$\Delta_{ij}^3 = Y_{ijn_{ij}} - Y_{ij1} \tag{3}$$

Equation (2) and (3) will allow us to see how the *evolution* of the hearing threshold differs for different age and side of the ear but will it not tell us anything about the *level* of the hearing threshold. To test whether the hearing threshold depends on age and side of the ear, equation (4) introduces Δ_{ij}^4 as the average measured hearing threshold for ear j of subject i. n_{ij} is the total number of measurements that were recorded for ear j of subject i.

$$\Delta_{ij}^4 = \frac{\sum_{t=1}^{t=n_{ij}} Y_{ijt}}{n_{ij}} \tag{4}$$

A first, obvious problem with this method is that it does not allow us to test all hypotheses of interest in one model. Additionally, a lot of information is lost:

- Only subjects with multiple measures on each ear are included in the summary measure of equation (2)
- Only ears that have been measured more than once are included in the summary measures of equation (3)
- Only subjects that were measured on both ears at a certain time instance are included in the summary measures of equation (1)
- While the summary measures of equation (2) and (3) can tell us something about the evolution in the long run because it focuses on the first and last measurement, all information on the trajectory between the first and last measurement is lost.
- Since the within-subject variability is rather large, relying on the first and last measurement as in equation (2) and (3) is risky.
- Previous literature found the hearing threshold was significantly higher for the first measurement (learning effect). Relying on the first measurement as in (2) and (3) may be worrisome.

To examine if the periodic shift in hearing capacity is affected by the patient's initial age and their time within the study, we examine their individual observed median absolute deviations (MAD) and their incremental shifts in hearing capability per year (SPY).

$$MAD = MEDIAN(|Y_{ijk} - \overline{Y_{ij}}|) \tag{5}$$

$$SPY = \frac{Y_{ijk_{max}} - Y_{ij1}}{TrialDuration} \tag{6}$$

The goal here is to see if patients of an older age or patients with a longer study period have larger degrees of variability in their hearing capacity. Examination of this relation could pose to provide insight into the nature of how hearing capability evolves over time. A positive relation between these metrics and a patients' starting age, in addition to their time spent in the study, would imply that hearing capabilities of older people have a more pronounced evolution compared to those of younger people. These variability measurements were taken in respect to both the left and right ears and then analyzed via an ANCOVA model.

2.2 Multivariate model

A multivariate model is constructed and we find the most parsimonious mean structure for it. Given the unbalanced data set, the *gee* and *geepack* packages are used to conduct Generalized Estimating Equations. We will conduct these under the strict assumptions of normality. We will compare models using Quasi-Information Criterium (QIC), the RMSE of the fitted residuals, and `ANOVA\MANOVA` tests. After some model searching in order to select the most parsimonious mean structure we will take care of selecting the appropriate covariance structure.

2.3 Two-stage analysis

In a two-stage analysis, subject-specific intercepts and time effects are first estimated. In the second step, these subject-specific parameters are analysed and related to additional covariates such as the age or the side of the ear.

2.4 Random-effects model

Lastly, a random-effects model is fit. This model is similar to the two-stage model but both stages are now combined in one model. We use the *nlme* package in R to fit the models.

3 Results

3.1 Summary statistics

First, a two-sided paired t-test is done, comparing the hearing threshold between the left and right ear. With a p-value of 0.44, there doesn't seem to be a significant difference between the hearing threshold for the left and right ear. Simple linear regression models that relate the age (on a continuous or discrete scale) to Δ_{it}^1 (equation (1)) also did not find any significant effects.

Next, regression models are made for Δ^2 and Δ^3. The variables of interest are age at the start of the study (a model with a continuous and discrete version is tested), the side of the ear (can only be tested for Δ^3), and the time difference between the first and last measurement (see Table 2). The intercept is always negative meaning the first measurement is higher than the

Table 2: Overview of the regression results for summary statistics

Variable	$\Delta^3_{continuous}$	$\Delta^3_{discrete}$	$\Delta^2_{continuous}$	$\Delta^2_{discrete}$
(Intercept)	-3.422 ***	-3.074 ***	-3.65 ***	-3.344 ***
age	0.089 ***		0.089 ***	
sideright	-0.197	-0.195		
timediff	0.32 ***	0.341 ***	0.332 ***	0.352 ***
age30-50		1.126		1.173
age50-70		3.248 ***		3.275 ***
age>70		5.338 ***		5.375 ***
Rsquared	0.085	0.098	0.114	0.132

Table 3: Overview of the regression results for summary statistics

Variable	$\Delta^4_{continuous}$	$\Delta^4_{discrete}$
(Intercept)	-5.858 ***	3.417 ***
age	0.254 ***	
sideright	0.071	0.049
age30-50		0.111
age50-70		5.841 ***
age>70		10.558 ***
Rsquared	0.242	0.226

last measurement in young subjects. This is unexpected and may be due to the learning effect that has been described in previous literature. Both age and the time between the first and last measurement have significantly positive coefficients meaning the difference between the first and last measurement is larger and may even become positive for older patients with long time between the first and last measurement. There is no significant difference between the left and right ear.

Table 3 shows the results for two regression models based on the summary statistic of equation (4). The age in this model refers to the age of the subject in the middle of his follow-up time (i.e. $age + \frac{max(TIME)}{2}$). The intercept now represents the expected hearing threshold for the left ear of a subject that is 0 years on (in the continuous age model) or a subject that is in the youngest age category (< 30 years old). The older the subject, the higher the expected hearing threshold. There is no significant difference between the left and right ear.

Table 4 details the results of the ANCOVA where the variance of the hearing capabilities. In agreement with the previously derived summary statistics, the starting age of the patient as well as their time spent within the study both have an effect on the MAD and SPY statistics. In further agreement with past results the side of the ear remains unimportant when inferring the expected

Table 4: Overview of the regression results for SPY and MAD summary statistics

Variable	MAD		SPY	
	Ancova Sum Sq.(Df)	lm coef	Ancova Sum Sq.(Df)	lm coef
(Intercept)	200.73***(1)	1.764***	41.299***(1)	-0.8***
StartingAge	174.406***(1)	0.024***	68.276***(1)	0.015***
duration	258.225***(1)	0.093***	19.857**(1)	0.026**
side	17.464 (1)	-0.278	0.276 (1)	-0.035
Residuals	6003.637(903)		2193.765(903)	

periodic change of subjects' hearing capabilities. From these results it can be stated that both age and the time spent within the study have a positive effect on the observed variance of the measured response. As was in the case with previous analyses, these results imply a potentially large shift in hearing capabilities over time. As was the case with previous analyses, their does not appear to be a significant difference between the two ears.

3.2 Multivariate model

We find that the model $Y_{ijk} = age_{ij} + age_{ij}^2 + learning_{ijk} + TIME_{ijk}$ performs really well and is congruent with what has been found before in the literature (model 2 in Table 5). We further find that the effect of the *side* variable does not significantly influence the hearing threshold. These conclusions hold for a much wider selection of models (we present here only sample of what we tested) or even when we filter the data under different conditions (Removing subjects with less than $n = \{2, 4, 5, 6\}$ observations, looking at only the right/left ear, treating each ear-subject pair as single subject, balancing the data, grouping the subjects in cohorts of $\{1, 5, 10, 15, 20\}$ years and creating dummy variables for them).

Now we will take a look at different covariance structures for the model (Table 5. Certain structures may lead to a stronger model fit, whereas others are inappropriate given the nature of our data. We will compare the same model mean structure i.e. $Y_{ijk} = age_{ij} + age_{ij}^2 + learning_{ijk} + TIME_{ijk}$ under different covariance structures and evaluate them according to Quasi Information Criterion (QIC) value. This is a performance metric which details the relative performance between a set of models.

It appears that a simple covariance structure that assumes independence across the variables produces the lowest QIC value, nevertheless it behooves us to take a closer look at these two models. First let's consider the model with a covariance structure that assumes equal covariances between variables with equivalent variances (compound symmetry).

In the Table 7, the model with compound symmetry correlation structure, we notice that we get two standard errors: Naive and Robust. Normally we would want to use the Robust estimates because the variances of coefficient estimates tend to be too small when responses within subjects are correlated (Bilder and Loughin 2014), however in this case there is little difference

Table 5: Comparison of multivariate models

	model1	model2	model3	model4	model5
(Intercept)	-4.735***	4.192	4.559.	-5.754***	-4.232***
age	0.237***	-0.175	-0.169	0.258***	0.251***
TIME	-0.048	-0.08	-0.111	0.199***	
learning		0.99*			
I(age^2)		0.004**	0.004**		
age:TIME	0.005	0.008*	0.007*		
sideright	0.259				
age:sideright	-0.005				
TIME:sideright	0.012				
QICu	336295.14	331467.63	331953.69	337007.96	341929.28
RMSE	6.54	6.54	6.46	6.56	6.59

Table 6: Comparison of multivariate models with an independent variance structure and a compound symmetry structure.

	independent / simple	compound symmetry
QIC	331510.00	332456.00
RMSE	6.45	6.49

Table 7: results for the model with compound symmetry

	Estimate	Naive S.E.	Naive z	Robust S.E.	Robust z
(Intercept)	5.8554196	2.6798986	2.184941	2.4579506	2.382236
age	-0.2354178	0.1130871	-2.081739	0.1111855	-2.117343
TIME	-0.1798128	0.0656499	-2.738964	0.0980970	-1.833010
learning	0.9662027	0.2580924	3.743631	0.3039955	3.178345
I(age^2)	0.0043943	0.0010841	4.053281	0.0011075	3.967781
age:TIME	0.0108198	0.0013002	8.321708	0.0021242	5.093568

Table 8: results for the model with independence

	Estimate	Naive S.E.	Naive z	Robust S.E.	Robust z
(Intercept)	4.1924228	1.3479365	3.1102524	2.7358254	1.5324161
age	-0.1754390	0.0542147	-3.2360035	0.1245143	-1.4089868
TIME	-0.0804050	0.0838418	-0.9590084	0.1326578	-0.6061083
learning	0.9898162	0.3882944	2.5491384	0.4257804	2.3247108
I(age^2)	0.0039222	0.0005086	7.7123744	0.0012335	3.1795734
age:TIME	0.0076767	0.0016615	4.6201967	0.0030550	2.5128535

Table 9: Second-stage results

model	intercept	age	age^2
Intercept	7.081 .	-0.253	0.004 **
TIME	-1.573 *	0.059 .	0
learning	-2.153	0.082	-0.001

between the Naive and Robust estimates. This further suggests that the independence assumption of the correlation structure seems realistic (Hothorn and Everitt 2009). Table 8 shows the best model we could find under the conditions of this task. It has the same parameter estimates as a least squares model with the same mean structure specification, however the robust errors in this model are more accurate, as some of the conditions of the least squares model are not fulfilled (e.g. Normally distributed residuals)

3.3   Two-stage analysis

As previous analyses showed that individuals may have a different time effect, the two-stage analysis first fits individual-specific intercept and time effect (slope). As all previous analyses did not uncover a significant effect of the side of the ear, it is no longer considered in this analysis.

The first stage analysis fits the linear model in equation (7); the variable *learning* is 1 if it's the first visit for the subject ($TIME == 0$). Next, the first stage results are used in the second stage (equation (8)) to relate the estimated subject-specific parameters to age.

$$Y_{ij} = \beta_{1i} + \beta_{2i}TIME_{ij} + \beta_{2i} * learning_{ij} + \varepsilon_{ij} \quad j = 1, ..., n_i \quad (7)$$

$$\begin{cases} \beta_{1i} = \beta_0 + \beta_1 age_i + \beta_2 age_i^2 + b_{1i} \\ \beta_{2i} = \beta_3 + \beta_4 age_i + \beta_5 age_i^2 + b_{2i} \end{cases} \quad (8)$$

Table 9 shows the results for the second stage. The first row shows estimates for β_0, β_1 and β_2. The estimated hearing threshold on the first visit for a person that is 0 years old is 7.081 -2.153 =

4.927dB and increases exponentially for each life year age^2 is highly significant. The expected slope increases with age (0.059 (p-value of 0.054)).

3.4 Random-effects model

Using what we have learned from the previous sections, and after test several models for the mean structure, we end up with the model $Y_{ijk} = age_{ij} + age_{ij}^2 + learning_{ijk} + TIME_{ijk}$ with a random slope and random intercept with id and $side$ as grouping variables (although there was no overall population effect of $side$, it appears that some peoples' left ear consistently scores better/worse than their right ear).

```
## Linear mixed-effects model fit by REML
##   Data: data
##   Log-restricted-likelihood: -14176.3
##   Fixed: y ~ age * TIME + learning + I(age^2)
##  (Intercept)          age         TIME     learning     I(age^2)     age:TIME
##  5.573984383 -0.222459295 -0.241154166  1.038379232  0.004242459  0.012325986
##
## Random effects:
##  Formula: ~1 + TIME | id
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev    Corr
## (Intercept) 6.7965362 (Intr)
## TIME        0.3845848 -0.183
##
##  Formula: ~1 + TIME | side %in% id
##  Structure: General positive-definite, Log-Cholesky parametrization
##             StdDev       Corr
## (Intercept) 2.1698486111 (Intr)
## TIME        0.0002151384 0
## Residual    4.7350438622
##
## Number of Observations: 4419
## Number of Groups:
##           id side %in% id
##          546         1086
```

After having selected the mean structure of the model we need to select the appropriate co-variance structure. We do so using a number of measures first with the help of our theoretical understanding, then using the AIC/QIC. Theoretical understanding helps us narrow the number of structures we need to test, for example Autoregressive or Toeplitz type structures are automatically excluded due to irregularities in the time intervals between measurements. For models (mixed model) which use the maximum likelihood we use the AIC. Although the AIC

is normally used to select the optimal model using the likelihood and penalizing the number of parameters, we use it to select the covariance structure. That is while holding the parameters the same but changing the covariance structure we see a decrease in the AIC only as a result of a higher likelihood. The same is done with the QIC but for models which use the Quasi maximum Likelihood. We observe that in the mixed model a simple covariance structure has better performance (AIC = 2.8378592×10^4) than using compound symmetry (AIC = 2.8380592×10^4).

4 Discussion and conclusion

We observe that on average men's hearing degrades as they get older. This happens in a slightly exponential manner, however when looking at it linearly, men increase their hearing threshold by about 0.25 decibels per year. Looking at it a bit more closely men younger than 55 increase their hearing threshold by about 0.22 decibels per year, while those above 55 do so by about 0.4 decibels per year. We do not see any difference between the left and right ear. Further we see that people with very good hearing to begin with are more sensitive to hearing loss as we see a slight negative correlation between random slopes and intercepts (-0.183).

4.1 Further research

We recommend that future experiments be conducted with a few but vital differences. First, we would recommend that each subject is measured at a fixed time interval. Presently the time difference between steps varies between measurements. Having measurements be done at a fixed interval would allow us to implement a wider selection of covariance structure to the models. Presently autoregressive or Toeplitz type covariance structures are not really applicable to the experimental design.

Secondly, we would recommend that there is a minimum number of measurements implemented per subject. As it stands there are subjects which were measured only once which greatly reduces the available methodology. We would recommend a minimum number of 4 (2 times for each ear) measurements per subject, with more measurements naturally being preferable.

Low number of observations could be to some extent be mitigated in an OLS type setting with the addition of a LASOO or RIDGE penalty. This naturally leads to an estimator which although not consistent, has a much smaller variance, which ultimately leads to a better performance. We are unsure if a LASOO or RIDGE regression is compatible with a mixed model type set up, where we calculate a separate LASOO/RIDGE penalty per subject. We hypothesize this type of methodology could also lead to a per subject variable selection in the LASOO case, which could be useful in problems with many independent variables with non-homogenous subjects. Further research is needed.

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