

Short Research Article

Evolution of Hearing Thresholds and the effect of Age

Abstract

Hearing loss is known to be a worldwide common problem caused by noise, aging, disease, and heredity. The aim of this study was to investigate how hearing thresholds evolve over time and how this evolution depends on age. Hearing thresholds were measured on 226 subjects the at different time-points and were categorized into normal (< 25 dB), mild ($25 - 40$ dB), moderate ($41 - 65$ dB) and severe (≥ 66 dB). A marginal model using Generalized Estimating Equations (GEE) and a generalized linear mixed model (GLMM) were fitted to the data. From both models it was observed that older subjects tend to have more hearing loss. In addition, from GLMM, it was noticed that the rate of decrease in hearing ability is larger for an older subject. This shows that the evolution of hearing loss depend on age at entry into the study. Empirical Bayes estimates were considered in GLMM to make inference about the random effects. It can be concluded that age has an effect on hearing thresholds and on their evolution over time.

Keywords: Hearing Thresholds, GEE, GLMM, Empirical Bayes

1 Introduction

Hearing loss is a common problem caused by noise, aging, disease, and heredity. It is a complex sense involving both the ear's ability to detect sounds and the brain's ability to interpret those sounds, including the sounds of speech. The hearing ability of an individual can be assessed through the hearing threshold, which is the minimum sound level of a pure tone that an average ear with normal hearing can hear with no other sound present [1]. In general clinicians measure the sound in dB HL (decibels Hearing Level), where thresholds between -10 and $+20$ dB HL are considered in the normal range and thresholds above 20 dB HL are considered diagnostic for mild, moderate, severe or profound hearing loss. To determine the hearing threshold, different type audiometers can be considered. A popular technique to measure the thresholds is known to be Bekesy [2] .

Worldwide, hearing loss affects more than 360 million people, being one of the most common conditions affecting older and elderly adults. Approximately one in three people between the ages of 65 and 74 has hearing loss and nearly half of those older than 75 have difficulty hearing. Frequently hearing loss is related to age, meaning that the hearing ability gradually reduces as an individual grows older. Moreover, age-related hearing loss can be caused by other issues such as: diabetes, poor circulation exposure to loud noise, family history of hearing loss, smoking, etc. [3,4]. The impact of hearing loss can be functional, social, emotional and economic depending on the individual and the level of the problem.

The main objective of this paper is to investigate how the hearing threshold evolves over time and how this evolution depends on age.

Section 2 of this report provides the description of the data and a brief discussion on marginal and random effects models focusing mainly on Generalized Estimating Equations (GEE) and Generalized Linear Mixed Models (GLMM) respectively. Next, results of the study are presented in section 3. Finally, in section 4 main conclusions are described and a brief discussion on transition models together with some suggestions for further research is given.

2 Methodology

2.1 Data and Variables

The data considered in this report consisted of 226 individuals who were submitted to a hearing test. Hearing thresholds (in dB) were measured over time at a frequency of 500 Hz, for the left ear only. In total 873 measurements were obtained. These measurements were taken in a sound-proof chamber, by means of a Bekesy audiometer. Negative values means that less than the initial signal was needed to be heard. The hearing thresholds were categorized into normal (< 25 dB), mild (25 - 40 dB), moderate (41 - 65 dB) and severe (≥ 66 dB). The choice is arbitrary and can be used for all subjects, since they are all adult [5] (Sharma, 2006). For each of the subject the identification number, time since entry in the study (in years), and age at entry in the study (in years) were collected.

2.2 Exploratory Data Analysis

In order to get more insight in the data, descriptive statistics were performed.

2.3 Marginal Models

Marginal models provide a straightforward way to extend generalized linear models to longitudinal data. They directly model the mean response at each occasion, $E(Y_{ij} | X_{ij})$, using an appropriate link function. Because the focus is on the marginal mean and its dependence on the covariates, marginal models do not necessarily require full distributional assumptions for the vector of repeated responses, only a regression model for the mean response [6] (Fitzmaurice *et al.*, 2009).

Within the frame of marginal model there are several approaches. These include full-likelihood, pseudo-likelihood and non-likelihood. In full-likelihood based approach the benefit is on the efficiency and also one can specify the joint probability. Nevertheless, the modelling of full-likelihood based models suffers from computational complexity and there is also an increased risk of model misspecification. Therefore, when one is interested in marginal mean parameters and pairwise interactions, a full likelihood procedure can be replaced by quasi-likelihood based methods. It is also worth mentioning that full-likelihood and quasi-likelihood methods coincide for exponential families and that the quasi-likelihood estimating equations provide consistent estimates of the regression parameters in any generalized linear model, even for choices of link and variance functions that do not correspond to exponential families [7] (Molenberghs and Verbeke, 2000).

Since likelihood based approaches are somewhat more difficult to formulate in non-Gaussian data, [8] proposed a more flexible semi-parametric approach, so-called Generalized Estimating Equations (GEE), which require only the correct specification of the univariate marginal distributions provided one is willing to adopt working assumptions about the association structure. It is worth noting that, GEE has the net benefit of yielding asymptotically and consistent estimates, even under wrong working correlation assumption [6]. Despite the existence of several type of GEE, in this report only the classical GEE, so-called GEE1 were considered.

The nature of the response variable in this report is multicategorical, and due to the fact that the interest is to study the marginal evolution of hearing threshold, GEE deemed appropriate to fit an averaged population model. Since there is a natural ordering in the response variable, proportional odds model was considered:

$$\text{logit}(Pr(Y_{ij} \leq c_j | Time_{ij}, Age_i)) = \beta_{0c} + \beta_1 Age_i + \beta_2 Time_{ij} + \beta_3 Age_i \times Time_{ij} ; c = 1, 2, 3 \quad (1)$$

Where Y_{ij} is the hearing loss at occasion j for subject i ; Age_i is the age of individual i at the time of entry into the study; and $Time_{ij}$ is the time point at which measurement j is taken for subject i . The β_i 's represent the regression parameters. $Time$ and age effects with powers larger than one were found not to be significant and therefore not considered as part of the mean structure. The model was only fitted using the independence working correlation structure due to lack of support of other correlation structures for ordinal data. Although the independence assumption is not realistic for the current setting, GEE correct for misspecification of the working correlation structure through the sandwich estimator [9].

2.4 Random Effects Models

Random effects models can be seen as a straightforward extension of generalized linear models by adding random effects. These random effects can be introduced in the probabilities directly or in the linear predictor. Due to the longitudinal nature of the data, the Generalized Linear Mixed Model (GLMM) is the most commonly used random effects model where random effects are added in the linear predictor to explain within-subject variability. To model the mean response at each occasion, it is conditioned upon the random effects, $E(Y_{ij} | X_{ij}, b_i)$. In contrast to marginal models, random effects models allow one to study the evolution of each subject separately and also predict the subject-specific evolution [7].

In GLMM the marginal likelihood is used as the basis for inferences about fixed parameters. In general, evaluation and maximization of the marginal likelihood for GLMMs requires integration over the distribution of the random effects. This also applies for the linear mixed-effects, but for the linear mixed model the integration can be done analytically, which means that there is a closed form for the marginal likelihood, implying that the application of maximum or restricted maximum likelihood is straightforward. In the absence of an analytical solution, and because high-dimensional numerical integration can be very difficult, a variety of approaches has been suggested for tackling this problem [6].

Since no closed form for the integral exists for non-gaussian response, different numerical approximations have been proposed: approximation of integrand (e.g Laplace approximation), approximation of data (e.g Penalized Quasi-Likelihood and Marginal Quasi-Likelihood), and approximation of the integral (e.g Adaptive and Non-Adaptive Gaussian Quadrature). Due to the fact that the data is discrete, the Laplace and Quasi-likelihood approaches yield quite biased estimators of the variance components, which leads to biased estimators of the fixed effect parameters and were therefore not considered. Adaptive Gaussian Quadrature, with numerical integration centered around empirical Bayes estimates of the random effects, allows maximization of the marginal likelihood with any desired degree of accuracy [6]. Taking this all into account, Adaptive Gaussian Quadrature was used to fit the random effects model.

As in the marginal case, the same proportional-odds model for hearing thresholds is considered by adding random effects to account for the within-subject association. A contrast test for common slopes was conducted to verify the proportional odds assumption [10]. The following random effects model was considered:

$$\text{logit}(Pr(Y_{ij} \leq c_j | Time_{ij}, Age_i)) = (\beta_{0c} + b_{0i}) + \beta_1 Age_i + \beta_2 Time_{ij} + \beta_3 Age_i \times Time_{ij}; \quad (2)$$

$c = 1, 2, 3$

Where b_{0i} represent the random intercept for subject i and for the other terms in the model the same notation applies as in the marginal model. The subject-specific random intercepts are assumed to be independent with $b_{0i} \sim N(0, \sigma_b^2)$ and are estimated by using empirical Bayes prediction.

2.5 Software

SAS 9.4 was used for statistical analysis and R 3.1.1 for graphical illustrations.

3 Results

3.1 Exploratory data analysis

From the 227 subjects who were involved in the study, data about hearing ability was missing for one individual (id = 224). The data was found to be highly unbalanced since the time-points were not commonly fixed for all individuals and unequally spaced.

The summary statistics of hearing loss at the start of the study are provided in Table 1 below. It is observed that the distribution of subjects across the categories is highly unbalanced with almost all subjects having a normal hearing ability and no individuals were found to have a severe hearing loss, since the largest hearing threshold was observed to be 46 dB which is less than the low limit of the severe category. The age of the individuals at the entry in the study ranges from 18.30 to 87 years, where the average age at the entry seems to be different for the three categories with older subjects having a larger amount of hearing loss on average at baseline.

Table 1: Summary statistics of hearing loss for the four categories at the first measurement

Hearing loss	Number of subjects	Average age
Normal	216	51.07
Mild	9	66.17
Moderate	1	73.50
Severe	-	-

The individual profiles of 40 randomly selected patients using continuous hearing score are displayed in Figure 1. From these profiles it is observed that there is a lot of between-subject and less, but still high, within-subject variability according to the evolution of hearing ability over time. Since there were large differences in hearing threshold at baseline, subject-specific intercepts for the individuals might be a good choice. However, age can also attribute to those differences in hearing thresholds at the start of the study.

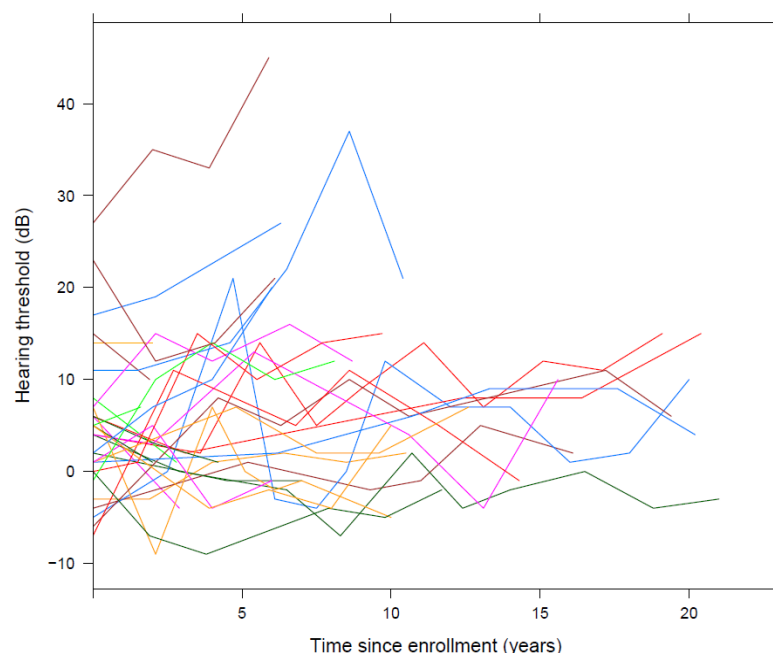


Figure 1: Individual profiles of 40 randomly selected subjects

3.2 Generalized Estimating Equations

In fitting the marginal model, the independence working correlation assumption was considered. In Table 2 the parameter estimates together with the empirically corrected standard errors are presented. Age of the subject at entry into the study showed a significant effect on the hearing loss.

It can be observed that older individuals have a higher probability of hearing loss ($\hat{\beta}_1 > 0$ and $\hat{\beta}_3 > 0$). Time and the interaction between age and time were found not to be significant, nevertheless it can be noticed that the decrease of hearing ability is faster for older patients.

Table 2: GEE parameter estimates with empirically corrected standard errors

Effect	Parameter	Estimate	Standard Error	P- value
Intercept 1	β_{01}	-9.4275	1.7165	< 0.000
Intercept 2	β_{02}	-7.1506	1.6252	< 0.000
Age	β_1	0.0680	0.0239	0.0044
Time	β_2	-0.0572	0.1643	0.7300
Age x Time	β_3	0.0023	0.0028	0.4000

3.3 Generalized Linear Mixed Model

It was observed that there is no evidence against the proportional odds assumption ($F = 2.33$, $P = 0.08$). The model summary statistics are presented in Table 3 by adaptive Gaussian quadrature with increasing accurate of approximation. It was noticed that the parameter estimates are more consistent and converse quickly by applying adaptive Gaussian quadrature. The GLMM with adaptive Gaussian quadrature approximation and Q equal to 50 were considered to be the final random effects model.

From the generalized linear mixed model it was also observed that Age of the subject at entry into the study had a significant effect on hearing ability. Condition on the subject, older individuals has a higher probability of hearing loss. Next, the interaction between Age and Time was found to be significant, as a borderline situation ($P = 0.04$). For a particular subject, the rate of decrease in hearing ability is larger when he or she is older. Time had no significant effect on the hearing thresholds. In addition, the variability of the random intercepts was about 6.51 and determines the size of deviation from the mean intercept as a source of within-subject variability.

Table 3: GLMM parameter estimates and standard errors by QUAD for various Q

		Q=5	Q=15	Q=50
Effect	Parameter	Estimate (s.e)	Estimate (s.e)	Estimate (s.e)
Intercept 1	β_{01}	-14.0643 (2.0330)	-14.5314 (2.1655)	-14.2880 (2.0800)
Intercept 2	β_{02}	-10.4739 (2.2101)	-10.8743 (2.3718)	-10.6856 (2.2705)
Age	β_1	0.0842 (0.0287)	0.0881 (0.0295)	0.0872 (0.0288)
Time	β_2	-0.3105 (0.2351)	-0.3192 (0.2385)	-0.3139 (0.2353)
Age x Time	β_3	0.0083 (0.0042)	0.0086 (0.0042)	0.0084 (0.0042)
var(b_i)	σ_b^2	6.3787 (2.2924)	7.1398 (2.8346)	6.5128 (2.4392)

In Table 4, a comparison of the parameter estimates and standard errors is presented for both marginal and random effects model under consideration. It was observed that the results for both model families were more or less similar, with same direction of effect. However, the estimates have a different interpretation and the estimates from the generalized linear mixed model were always bigger in magnitude.

Table 4: Parameter estimates (standard errors) for marginal model (GEE1) and random effects model (GLMM) with QUAD integration (Q=50) together with ratio of both sets of parameters and standard errors

Effect	Parameter	GEE1	GLMM	Ratio
Intercept 1	β_{01}	-9.4275 (1.7165)	-14.2880 (2.0800)	1.5156; 1.2118
Intercept 2	β_{02}	-7.1506 (1.6252)	-10.6856 (2.2705)	1.4944; 1.3971
Age	β_1	0.0680 (0.0239)	0.0872 (0.0288)	1.2824; 1.2050
Time	β_2	-0.0572 (0.1643)	-0.3139 (0.2353)	5.4878; 1.4321
Age x Time	β_3	0.0023 (0.0028)	0.0084 (0.0042)	3.6522; 1.5000

3.4 Empirical Bayes Estimates

A plot for the empirical Bayes estimates b_i of the random intercepts is shown in Figure 2. It was observed that there is a lot of shrinkage towards the prior mean of the random intercepts (zero). Besides, there were some outliers detected in the estimates. A histogram plot of the estimates of random intercepts is shown in Figure A1. Same conclusions can be made since almost all random intercepts were estimated to be zero and a few outliers were found, especially negative estimates.

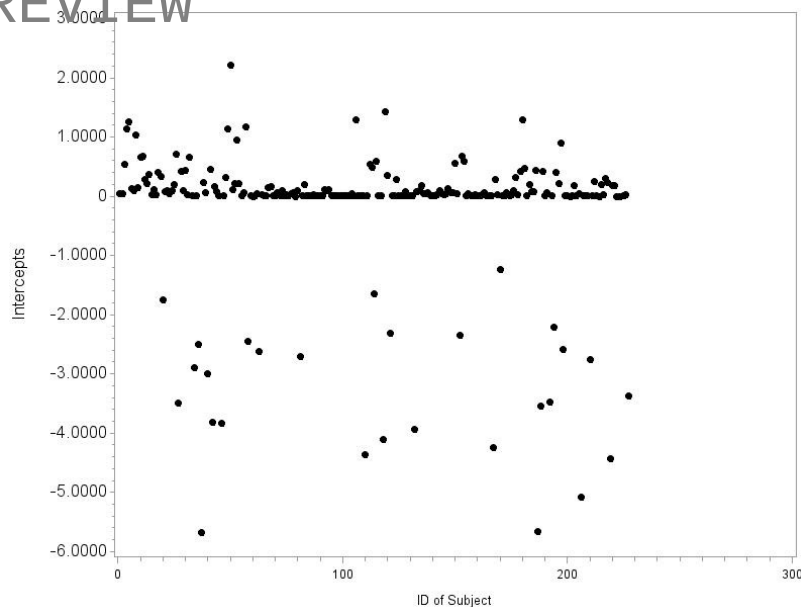


Figure 2: Distribution of empirical Bayes estimates of random intercepts (b_i)

4 Discussion and Conclusions

The aim of this paper was to investigate how hearing thresholds evolve over time and how these evolutions depended on age. Since missing data was observed, the measurements were not taken at fixed time points and the time between measurements were not equally spaced, methodologies that can deal with the longitudinal nature of the unbalanced data were required in order to provide meaningful results. The hearing thresholds were quatrictomized into different categories: normal (< 25 dB), mild ($25 - 40$ dB), moderate ($41 - 65$ dB) and severe (≥ 66 dB).

Extensions of generalized linear models using logit link were considered as a way to deal with discrete longitudinal data. First, a marginal model using GEE1 method to obtain population-averaged estimates was fitted under independence working correlation structure. Although the choice of working assumption could be found as unrealistic due to the longitudinal nature of the data, a misspecification of the correlation structure would not harm the parameter estimates of interest [6]. It was observed that at a certain time on average older individuals have higher probabilities of hearing loss. This is supported by [3] where hearing loss was found to be age-related. It was also noticed that the decrease of hearing ability was faster for older patients, though it was not found to be significant. Further, time was not found to have an effect on hearing thresholds. Since the interest is based on the average population, the marginal model is preferable and provides us the parameters of interest. The advantage of GEE is that it only requires a correct specification of the univariate marginal distributions by assuming a working assumption about the correlation structure such that the parameters could be estimated without making full distributional assumptions [9].

As a random effects model, generalized linear mixed model was fitted using random intercepts to account for within-subject variability. The final random effect model was considered as the generalized linear mixed model using numerical integration (Adaptive Gaussian quadrature with 50 quadrature points). While the marginal model had the focus on the population-averaged evolution of hearing thresholds depending on age, the random effects model has the benefit to draw inferences on the subject-specific evolution of hearing thresholds [7]. Although the parameter estimates for the marginal model and random effects model cannot be compared, similar directions of effects were noticed. However, in the generalized linear mixed model it was found that the rate of decrease in hearing ability is larger for an older subject, condition on the random effects. In both models age had an effect on the hearing loss, with increasing hearing loss when the age of a subject increases.

In magnitude the parameter estimates and standard errors obtained by GEE in the marginal model was smaller compared to those obtained from the generalized linear mixed model.

In GLMM, as well as in the linear mixed model, empirical Bayes estimates are used to make inference about the random effects. Although most of the time the interest is in the fixed-effects parameters, empirical Bayes estimates can be used to make prediction on the random effects. Moreover, one can use empirical Bayes estimates to study the subject specific profile or to make prediction of the subject-specific evolution. For linear mixed-effects models with the classical normal assumption for the random effects, deviations from the normality assumption for the random effects have very little impact on the estimation of the fixed-effects parameters. On the other hand, in GLMM misspecification of the random-effects distribution can lead to seriously biased estimates for the fixed-effects parameters. However, there is no formal test to check the validity of the normality assumption, since this could be a result of the fact that the prior distribution dominates the posterior (shrinkage towards the prior mean of the random intercept), which is probably the case in this study due to missingness. Moreover, empirical Bayes estimates can be useful for identifying outlying observations [6].

Another way to deal with longitudinal data is by considering transition models as a special class of conditional models where the conditional distribution of the response at any occasion is modelled given a set of previous responses and the covariates [6]. Transition models assume the Markov structure for the longitudinal process to encompass the correlating among the repeated measures [11]. However, transition models have been criticized because the interpretation of fixed effect parameters is conditioned on the previous measurements. In addition, transition models have limitations that it is applicable for repeated measures that are equally separated over time, but more difficult to apply when there are missing data, mistimed measurements, and non-equidistant intervals between measurement occasions [8]. Moreover, estimation of the regression parameters is very sensitive to assumptions concerning the time dependence and the interpretation changes with the order of serial dependence. Based on these arguments and due to the fact that the number of measurements per subject regarding hearing threshold were not equal and the time points at which the measurements were taken were not equally spaced, transitional models were deemed not appropriate and were therefore not considered.

Some limitations could be taken into account for improvement. First, the marginal model with GEE was fitted assuming a strong assumption of MCAR. However, patterns in missingness could be explored in order to define whether techniques such as weighted GEE or multiple imputation could be considered [6] to provide an appropriate analysis technique for incomplete data. In addition, only a few individuals were found to have mild, moderate or severe hearing loss. Therefore, quatrachotomization might not be the best choice to analyse hearing thresholds. Finally other important factors that can be studied related to hearing thresholds, such as gender or other causes of hearing loss, can be considered to reduce the between-subject variability.

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Appendix

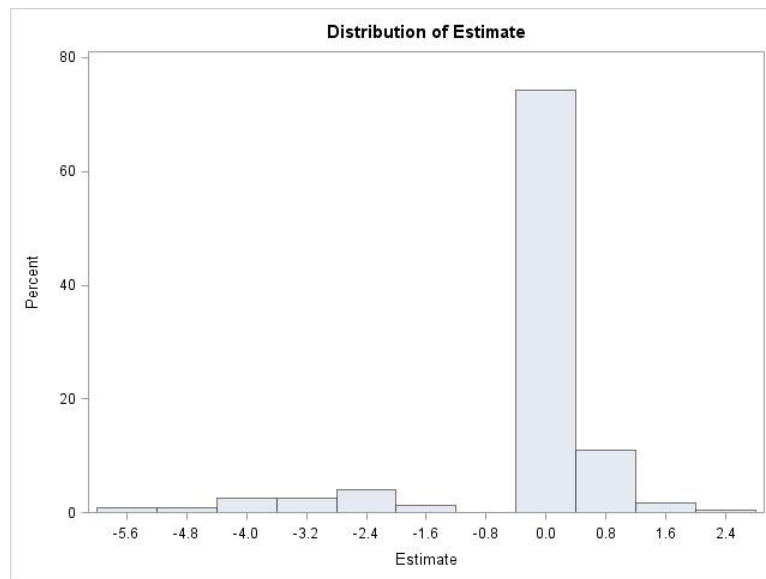


Figure A1: Histogram of empirical Bayes estimates of random intercepts (b_i)