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Joint modelling of multivariate longitudinal profiles: pitfalls of the random-effects approach

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SUMMARY

Due to its flexibility, the random-effects approach for the joint modelling of multivariate longitudinal profiles received a lot of attention in recent publications. In this approach different mixed models are joined by specifying a common distribution for their random-effects. Parameter estimates of this common distribution can then be used to evaluate the relation between the different responses. Using bivariate longitudinal measurements on pure-tone hearing thresholds, it will be shown that such a random-effects approach can yield misleading results for evaluating this relationship. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS: joint modelling; multivariate longitudinal profiles; mixed models

1. INTRODUCTION

Multivariate longitudinal data arise when a set of different responses on the same unit are measured repeatedly over time. An example of a research question for such data is how the evolution of one response is related to the evolution of another response ('association of the evolutions'). A seemingly related, but different question is how the association between responses evolves over time ('evolution of the association'). To answer such research questions a joint modelling strategy is needed.

Different joint modelling approaches exist. In the first class of models, one response is analysed while conditioning on other responses. Examples of such an approach can be found in the extensive literature on jointly analysing a marker process with a survival outcome [1, 2]. The disadvantage of this approach in the present context is that one has to choose a response to condition on. This also implies that additional computations are needed to derive information on the marginal responses or on the marginal associations. In a second class of possible models a marginal model for each response is specified and these marginal models are then joined in one or another way. Catalano and Ryan [3] used the concept of

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a latent variable to derive the joint distribution of bivariate clustered data of different types. The treatment effect is then described as an effect on the underlying latent variables. As an alternative to estimate a treatment effect and to avoid the need to assume existence of an unobservable latent variable, Gray and Brookmeyer [4, 5] proposed a model where a scale-aspecific treatment effect is characterized as an acceleration or decelaration of the time scale. Another way to join marginal models is using copulas [6].

However, none of these approaches answers the question of how the evolution of one response is related to the evolution of another response. A flexible solution is to model the association between the different responses using random effects. In applied sciences, random-effects models have become the preferred tool to analyse various types of longitudinal data. With these models, the average evolution of a specific response is described using some function of time, and subject-specific deviations from this average evolution are introduced by using so-called random effects. The introduction by Laird and Ware [7] of the linear mixed model, devised for continuous data, has been followed rapidly by extensions to deal with non-linear data (non-linear mixed effects model, [8]) and with non-continuous measurements (generalized linear mixed model, [9]). In a joint-modelling approach using mixed models, random-effects are assumed for each response process and by imposing a joint multivariate distribution on the random effects, the different processes are associated. This approach has many advantages and is applicable in a wide variety of situations. Indeed, the approach allows to join models for responses of the same response type as well as models for responses of different types. The approach has been used in a non-longitudinal setting to validate surrogate endpoints in meta-analyses [10, 11] or to model multivariate clustered data [12]. Gueorguieva [13] used the approach for the joint modelling of a continuous and a binary outcome measure in a developmental toxicity study on mice. Also in a longitudinal setting, Chakraborty *et al.* [14] obtained estimates of the correlation between blood and semen HIV-1 RNA by using a joint random-effects model. Other examples with longitudinal studies can be found in References [15–18]. Zucker *et al.* [19] proposed a multivariate growth curve model to make inferences on the association between evolutions. Williams [20] used this approach to model simultaneously growth curves for systolic and diastolic blood pressure, height and BMI. However, such a modelling strategy is restricted to the combination of outcomes of the same type.

Using bivariate data on pure-tone hearing thresholds, the random-effects approach will be critically investigated. Section 2 introduces this data set, presents a univariate model and illustrates the two research questions. Section 3 describes the multivariate random-effects approach and details the bivariate case. Section 4 applies the approach on the hearing data and investigates the obtained results for the evolution of the association and the association of the evolutions, respectively. Section 5 evaluates the impact of the conditional independence assumption on the obtained results. Section 6 contains a discussion.

2. HEARING DATA

In a hearing test, the hearing threshold sound pressure levels (dB) are determined at different frequencies to evaluate the hearing performance of a subject. A hearing treshold is the lowest signal intensity a subject can detect at a specific frequency. In this study, hearing thresholds measured at two different frequencies (500 and 1000 Hz), obtained on 347 male participants

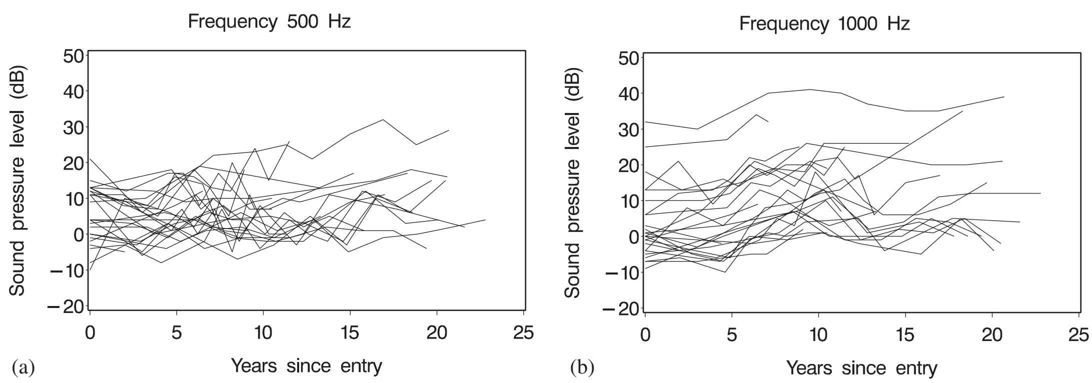

Figure 1. Individual profiles of hearing tresholds for 500 and 1000 Hz (of 30 randomly selected subjects).

in the Baltimore longitudinal study of aging (BLSA) [21] are considered. Analyses of the hearing data collected in the BLSA study can be found in References [22–24]. The analyses presented in this paper are restricted to participants with at least 4 visits. The reason for this restriction will become clear in the remainder of the paper. The age at first visit ranged from 17.2 to 90.5 years with median value equal to 48.6 years. The number of visits per subject varied from 4 to 15 with a median follow-up time of 15.2 years. Visits are unequally spaced. Only results on the left ear are considered in this paper. Individual profiles for the two different frequencies are shown in Figure 1.

Verbeke and Molenberghs [25] proposed the following linear mixed model to analyse the evolution of the hearing threshold for a single frequency. Let $Y_i(t)$ denote the hearing threshold at some frequency for a subject i taken at time t, the model is specified as

$$\begin{aligned} Y_i(t) = {} & (\beta_1 + \beta_2 \text{Age}_i + \beta_3 \text{Age}_i^2 + a_i) \\ & + (\beta_4 + \beta_5 \text{Age}_i + b_i)t \\ & + \beta_6 \text{Visit1}_i + \varepsilon_i(t) \end{aligned} \tag{1}$$

in which t is time expressed in years from entry in the study and Age_i is the age of subject i at the time of entry in the study. Since there is evidence for the presence of a learning effect from the first to the subsequent visits, a time-varying covariate Visit1_i has been added. This covariate is defined to be one at the first measurement and zero for all other visits. Finally, the a_i are random intercepts, the b_i the random slopes for time and the ε_i the usual error components. The vector $(\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6)'$ of fixed effects describes the average evolution of the hearing threshold and the vector $(a_i, b_i)'$ of random effects describes how the profile of the ith subject deviates from the average profile. The classical normality assumptions apply for all random terms in this model. Two different research questions need to be answered:

1. How does the association between the hearing tresholds for frequencies 500 and 1000 Hz evolve over time?
2. How are the evolutions in hearing threshold for frequencies 500 and 1000 Hz associated?

In the next section, a joint modelling strategy is presented to answer both these questions.

3. JOINT MODELLING: RANDOM-EFFECTS APPROACH

In the context of jointly modelling two frequencies, let $Y_{1i}(t)$ and $Y_{2i}(t)$ denote the hearing thresholds of two frequencies for a subject i taken at time t. Each hearing threshold is described using the linear mixed-effects model (1)

$$\begin{aligned} Y_{1i}(t) &= \mu_1(t) + a_{1i} + b_{1i}t + \varepsilon_{1i}(t) \\ Y_{2i}(t) &= \mu_2(t) + a_{2i} + b_{2i}t + \varepsilon_{2i}(t) \end{aligned}$$

where $\mu_1(t)$ and $\mu_2(t)$ refer to the average evolutions. Both response trajectories are tied together through a joint distribution for the random effects

$$\begin{bmatrix} a_{1i} \\ a_{2i} \\ b_{1i} \\ b_{2i} \end{bmatrix} \sim N(\mathbf{0}, \boldsymbol{D})$$

where $\boldsymbol{D}$, the covariance matrix of the random effects, has the following structure:

$$\begin{bmatrix} \sigma_{a_1}^2 & \sigma_{a_1a_2} & \sigma_{a_1b_1} & \sigma_{a_1b_2} \\ & \sigma_{a_2}^2 & \sigma_{a_2b_1} & \sigma_{a_2b_2} \\ & & \sigma_{b_1}^2 & \sigma_{b_1b_2} \\ & & & \sigma_{b_2}^2 \end{bmatrix}$$

The error components are uncorrelated and not associated with the random effects

$$\begin{bmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{bmatrix} \right)$$

The latter implies that conditional on the random effects, both response trajectories are independent. Special cases can now be obtained from making additional assumptions about the covariance matrix $\boldsymbol{D}$. For example, if $\sigma_{a_1a_2}$, $\sigma_{a_1b_2}$, $\sigma_{b_1a_2}$ and $\sigma_{b_1b_2}$, are all equal to zero, both frequencies are assumed to be completely independent at any point of time. The opposite situation applies when some of the enumerated covariance parameters lead to unit correlations. For example, the random slopes for 500 Hz can be perfectly correlated with the random slopes for 1000 Hz. We then have a so-called shared-parameter model [26]. Parameters of the model can be obtained using likelihood based inference, with e.g. the SAS-procedure PROC MIXED. Note that PROC NLMIXED can be used for the random-effects approach to combine models for non-continuous response types or to combine models with different response types.

The answer to the question how the evolution of the hearing threshold for 500 Hz is associated with the evolution of the hearing threshold for 1000 Hz is typically derived from the covariance matrix of the random effects. Indeed, the correlation between both evolutions (r_{E}) is given by

$$r_{\mathrm{E}} = \frac{\sigma_{b_1 b_2}}{\sqrt{\sigma_{b_1}^2}\sqrt{\sigma_{b_2}^2}} \tag{2}$$

Using the outlined random-effects approach, the marginal correlation between both frequencies as a function of time is given by

$$r_{\mathrm{M}}(t) = \frac{\sigma_{a_1 a_2} + t\sigma_{a_1 b_2} + t\sigma_{a_2 b_1} + t^2\sigma_{b_1 b_2}}{\sqrt{\sigma_{a_1}^2 + 2t\sigma_{a_1 b_1} + t^2\sigma_{b_1}^2 + \sigma_1^2}\sqrt{\sigma_{a_2}^2 + 2t\sigma_{a_2 b_2} + t^2\sigma_{b_2}^2 + \sigma_2^2}} \tag{3}$$

Using the delta rule [27] confidence bounds can be obtained for $r_{\mathrm{M}}(t)$ for any particular time point t. When $t = 0$ the marginal correlation simplifies as

$$r_{\mathrm{M}}(t) = \frac{\sigma_{a_1 a_2}}{\sqrt{\sigma_{a_1}^2 + \sigma_1^2}\sqrt{\sigma_{a_2}^2 + \sigma_2^2}}$$

which implies that the absolute value of the marginal correlation at $t = 0$ cannot be higher than the correlation between the random intercepts. The smaller the measurement errors of both frequencies, the closer the marginal correlation at $t = 0$ approximates the correlation between the random intercepts. Moreover, when t increases the marginal correlation converges to the correlation between the random slopes. It is important to note that the covariance parameters of the random effects (together with the variances of the error components) determine the shape of the marginal correlation function.

4. RESULTS

The two independent univariate models can be fitted as a joint model with appropriate covariance terms equal to zero. The corresponding loglikelihood value and AIC are -15759.5 and 31535.0, respectively. Allowing non-zero covariances between the random effects further increased the loglikelihood to -15592.45 (AIC $= 31208.9$). A likelihood-ratio test ($\chi^2 = 334.1$, $df = 4$) rejects the use of two independent models ($p < 0.0001$). The obtained parameter estimates for the covariance parameters in the model can be found in Table I.

4.1. Evolution of the association

To verify to what extent the implied marginal correlation function is compatible with the observed data, an indication of the observed marginal correlation is needed. Since the time-intervals between successive measurements differ between subjects, the 'observed' marginal correlation cannot be obtained directly by calculating an index of association at each time point and evaluating its evolution. To circumvent this problem, a 'moving window' technique has been applied. A correlation coefficient has been calculated on a subset of the data, defined by the width of the window (taken as 2 years). Moving this window over the time axis by small steps (0.1 year) yields the marginal correlation function. Figure 2 plots the so-obtained observed marginal correlation compared with the marginal correlation implied by the random-effects approach. It can be clearly seen that the implied marginal correlation is increasing,

Table I. REML estimates for the covariance parameters in the univariate model, the bivariate random-effects model with uncorrelated errors, and the bivariate random-effects model with correlated errors (ll = loglikelihood, AIC = Akaike's information criterion).

	Univariate model	Bivariate model: Uncorrelated error	Bivariate model: Correlated error
ll	−15759.5	−15592.45	−15484.9
AIC	31535.0	31208.9	30995.8
$\sigma^2_{a_1}$	40.34	40.11	40.17
$\sigma_{a_1a_2}$	—	44.58	41.63
$\sigma^2_{a_2}$	71.86	71.86	72.03
$\sigma_{a_1b_1}$	0.077	0.043	0.064
$\sigma_{a_2b_1}$	—	−0.046	0.179
$\sigma^2_{b_1}$	0.069	0.083	0.074
$\sigma_{a_1b_2}$	—	−0.414	−0.147
$\sigma_{a_2b_2}$	0.004	−0.001	−0.007
$\sigma_{b_1b_2}$	—	0.098	0.062
$\sigma^2_{b_2}$	0.123	0.135	0.125
σ^2_1	23.77	23.55	23.71
σ^2_2	22.97	22.79	22.95
σ_{12}	—	—	7.89

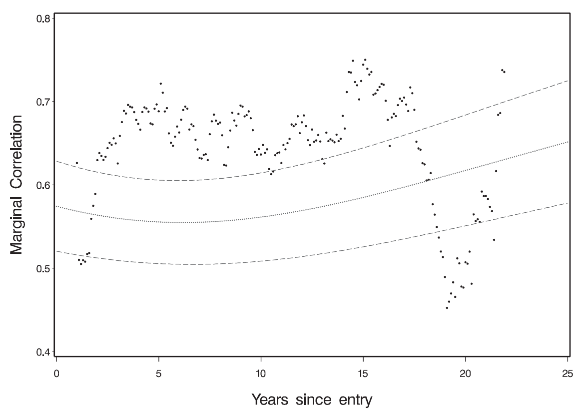

Figure 2. Comparison of observed (dots) and implied (solid line) marginal correlation. The dashed lines represent a 95 per cent confidence band for the implied marginal correlation function, obtained using the delta method. The implied correlation is derived from the bivariate model with uncorrelated errors.

whereas the observed correlation does not follow this pattern. Moreover, a substantive part of the observed marginal correlations falls outside the confidence band of the implied marginal correlation function.

Note that the correlations in Figure 2 have been calculated on OLS residuals, obtained by fitting the joint model, but by assuming independence of all observations. These residuals can

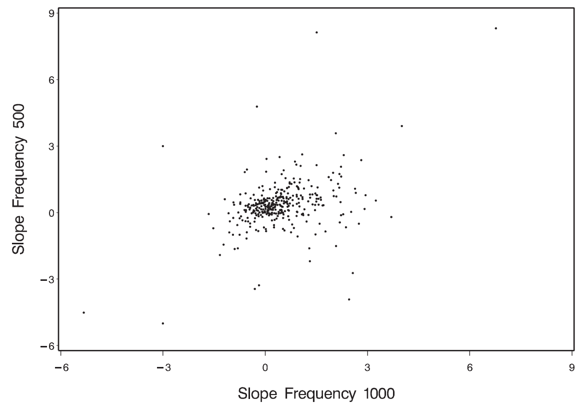

Figure 3. Slopes for both frequencies obtained with subject-specific regression models.

be used since it follows from the theory of generalized estimating equations (GEE) that the OLS estimator is consistent [28]. Some subjects will contribute more than one observation per frequency in the calculation of one observed marginal correlation (one dot in Figure 2), which will affect the precision of the estimated correlation. Therefore, the comparison between the observed and the implied marginal correlation is based on the confidence band for the implied marginal correlation function (calculated from the fitted bivariate model) and not on confidence intervals for the observed marginal correlations.

4.2. Association of the evolutions

Applying expression (2) on the covariance estimates in Table I yields 0.929 as correlation between the slope for frequency 500 and the slope for frequency 1000, which suggests a strong positive association between the evolutions of both hearing thresholds. The profile likelihood based 95 per cent confidence interval for this correlation equals (0.788; 1).

A two-stage analysis has been performed to verify if the association implied by the joint model is reasonable. In the first stage, a linear regression model has been fitted for each subject separately to obtain estimates of the subject-specific slopes for both frequencies. For a single frequency, this first-stage model is specified as

$$Y_i(t) = \beta_{1i} + \beta_{4i}t + \beta_{6i}\text{visit1}_i + \varepsilon_i(t) \tag{4}$$

where, in accordance with the subscripts in model (1), β_{1i}, β_{4i} and β_{6i} refer to a subject-specific intercept, slope and first-visit effect, respectively. The ε_i are normally distributed error components. Adding an additional subscript, let β_{41i} and β_{42i} denote the subject-specific slopes for the first and the second frequency, respectively. Figure 3 gives a scatterplot of the estimated slopes. In a second stage, the correlation between these subject-specific slopes can be calculated. With known β_{41i} and β_{42i}, the correlation between the slopes could be derived from the model

$$\begin{bmatrix} \beta_{41i} \\ \beta_{42i} \end{bmatrix} = \begin{bmatrix} \beta_{51}\text{Age}_i \\ \beta_{52}\text{Age}_i \end{bmatrix} + \begin{bmatrix} \beta_{41} \\ \beta_{42} \end{bmatrix} + \begin{bmatrix} b_{1i} \\ b_{2i} \end{bmatrix} \tag{5}$$

where the last term on the right-hand side follows a zero-mean normal distribution with dispersion matrix G, from which the required correlation can easily be derived. β_{51} and β_{52} denote the effect of age at entry in the study for the first and second frequency, respectively. These terms are included in model (5) since the joint random-effects model contains an interaction between age at entry in the study and time. In practice, only estimates for β_{41i} and β_{42i}, derived from fitting the subject-specific regression models, are available. Therefore, using model (5) on the estimated slopes will yield a biased correlation due to the measurement error involved in the estimation of β_{41i} and β_{42i} [29]. To see this more formally [11] assume the following model for the estimated slopes $\hat{\beta}_{41i}$ and $\hat{\beta}_{42i}$

$$\begin{bmatrix} \hat{\beta}_{41i} \\ \hat{\beta}_{42i} \end{bmatrix} = \begin{bmatrix} \beta_{41i} \\ \beta_{42i} \end{bmatrix} + \begin{bmatrix} \omega_{1i} \\ \omega_{2i} \end{bmatrix} \tag{6}$$

where the estimation errors ω_{1i} and ω_{2i} follow a zero-mean bivariate normal distribution with dispersion matrix Ω_i. Assuming these estimation errors being independent from $(b_{1i}, b_{2i})'$ in model (5), the vector with the estimated slopes $(\hat{\beta}_{41i}, \hat{\beta}_{42i})'$ follows a normal distribution with mean $(\beta_{41i}, \beta_{42i})'$ and covariance matrix $G+\Omega_i$. The covariance matrices Ω_i are assumed to be known and equal to the estimates obtained from the subjects-specific regression models fitted in the first stage. From the elements in G, the bias-corrected correlation between the slopes can be calculated. Notice that due to the different number of measurements per subject, it is reasonable to allow that the measurement error can vary between individuals. Therefore, the covariance matrix Ω has a subscript i. The previously discussed approach to adjust for the bias is outlined in [30].

The unadjusted correlation between $\hat{\beta}_{41i}$ and $\hat{\beta}_{42i}$ equals 0.385, whereas the adjusted correlation equals 0.705, with (0.576; 0.799) as profile likelihood based 95 per cent confidence interval. Comparing this interval with the correlation obtained by the joint model ($R_{\mathrm{E}} = 0.929$), it is clear that the random-effects approach overestimates the strength of the association between the evolutions of both frequencies.

5. RELAXING THE CONDITIONAL INDEPENDENCE ASSUMPTION

Note that in the presented joint model the two frequencies are only tied together by their random-effects distribution, implying that—in accordance with common choices in the literature–independent measurement errors were assumed. Otherwise said, the responses of both frequencies are independent and conditional on the random effects. However, the question remains if this assumption is not too restrictive, yielding an inappropriate model for the covariance structure of the joint model. Relaxing this conditional independence assumption induces an additional covariance parameter σ_{12} referring to the covariance between the error components. This implies that the marginal correlation becomes

$$r_{\mathrm{M}}(t) = \frac{\sigma_{a_1a_2} + t\sigma_{a_1b_2} + t\sigma_{a_2b_1} + t^2\sigma_{b_1b_2} + \sigma_{12}}{\sqrt{\sigma_{a_1}^2 + 2t\sigma_{a_1b_1} + t^2\sigma_{b_1}^2 + \sigma_1^2}\sqrt{\sigma_{a_2}^2 + 2t\sigma_{a_2b_2} + t^2\sigma_{b_2}^2 + \sigma_2^2}} \tag{7}$$

while the formula for the correlation between the evolutions R_{E} in (2) remains the same.

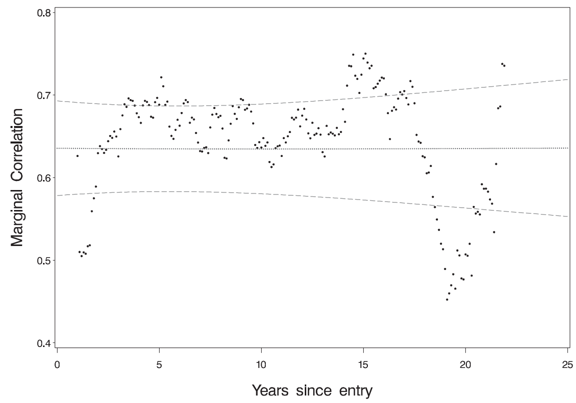

Figure 4. Comparison of observed (dots) and implied (solid line) marginal correlation. The dashed lines represent a 95 per cent confidence band for the implied marginal correlation function. The implied correlation is derived from the bivariate model with correlated errors.

Fitting the joint model but now allowing for correlated errors increases the loglikelihood from -15592.45 (AIC = 31208.9) to -15484.9 (AIC = 30995.8). A likelihood-ratio test ($\chi^2 = 215.1$, $df = 1$) rejects the conditional independence assumption ($p < 0.0001$).The obtained parameter estimates for the covariance parameters in this joint model can also be found in Table I.

5.1. Evolution of the association

Figure 4 plots the observed marginal correlation compared with the marginal correlation implied by the joint model with correlated errors. Comparing this figure with Figure 2, it can be clearly seen that the form of the implied marginal correlation has changed. Moreover, the major part of the observed marginal correlations lies inside the confidence band of the implied marginal correlation function.

5.2. Association of the evolutions

As before, to obtain the correlation between the evolutions using the joint model, expression (2) has been applied on the covariance estimates in Table I. This yields 0.643 as correlation between the slope for frequency 500 and the slope for frequency 1000 Hz, with (0.478; 0.775) as 95 per cent profile likelihood based confidence interval. Hence, by allowing a correlated structure for the error components, the result derived from the joint model is in accordance with the two-stage approach.

6. DISCUSSION

There are several advantages of using random-effects models for joint modelling purposes. First, the different responses do not necessarily need to be of the same type (continuous/discrete). Second, these models can be easily implemented in standard software, such as SAS procedure MIXED in case of only continuous outcomes, or SAS procedure NLMIXED for the analysis of discrete outcomes or mixed continuous/discrete outcomes. Third, the different responses neither need to be measured at the same time points, nor does one have to assume that the same number of repeated measurements is available for all outcomes. Fourth, the approach gives an immediate indication of the association between different evolutions. Finally, using some additional computations the evolution of the association can easily be derived from the obtained parameter estimates.

In this paper, a joint model using random-effects was used in a bivariate setting with longitudinally measured continuous outcomes. The two outcomes were tied together by a common distribution for the random intercepts and slopes, implying independence conditional on the random effects. The aim of the joint model was to study the relation between two hearing thresholds. Two aspects of the relation were investigated: the association between the evolutions and the evolution of the association. Results of the joint model suggested a very strong association between the evolutions and a slowly increasing evolution of the association. The latter result stems from the convergence of the marginal correlation r_{M} to the high correlation between the slopes. The validity of the joint model has been verified for two aspects of the relation between the outcomes. With respect to the association between the evolutions, a two-stage approach has been applied. In the first stage, subject-specific regression models have been used to obtain estimates for the slopes for both frequencies. In the second stage, the correlation between the estimates has been calculated taking into account the bias induced by the measurement error of the estimation procedure in the first stage. A two-stage procedure to estimate the correlation between evolutions in a longitudinal study has been proposed already by Schluchter [29]. To assess the validity of the evolution of the association, a pattern of correlations using a moving window technique on the observed data has been used as reference. The results indicated a discrepancy between the data and the relations implied by the joint model, for the association of the evolutions as well as for the evolution of the association. It can therefore be misleading to overinterprete the results on the relationship between outcomes implied by the joint random-effects model.

However, relaxing the conditional independence assumption by allowing correlated errors revealed that the discrepancy was due to the inappropriate modelling of the covariance structure. This indicates that the answer to a question which does not refer to the error structure, can highly be influenced by assumptions made on the error components. This is especially surprising for the association of the evolutions, since the covariance parameters for the error components are not used in its calculation. In the context of clustered bivariate outcomes, Gueorguieva [13] introduced conditional dependence by including one response in the predictor for the other response and presented a score test to check the validity of the conditional independence assumption. In another analysis on the same data set (2001b) the conditional dependence was induced by allowing error correlation. It is obvious that the need for scrutinizing the covariance structures depends on the aim of the joint modelling analysis. Two situations should be distinguished. In the first situation, primary interest is in gaining efficiency for the estimation of the fixed effects in the model, in analysing fixed effects simultaneously or the comparison of different outcomes (as in e.g. References [13, 31]). Although problems might occur due to under- or overparameterization of the covariance structure [25], it is obvious that the interpretation of the fixed- effect parameters themselves remain the same. In the second situation, the covariance structure itself is of interest [17], as was the case in our application. The interpretation of a covariance parameter then depends on the set of other covariance parameters in the model. A similar finding is made for univariate longitudinal mixed models where inclusion of serial correlation induces competition between sources of stochastic variation [25].

Besides relaxing the conditional independence assumption as has been done in Section 5, other extensions of the joint random-effects model presented in Section 3 are possible. One referee suggested that serial correlation can be imposed on the error processes over time, with or without correlation between the two frequency-specific autoregressive series (e.g. Reference [32]). The expression for the marginal correlation between both frequencies (expression 3) will then change according to the type of extension, while the correlation between the evolutions is still given by the appropriate elements in the random-effects covariance matrix D. Nevertheless, the estimate for D will be influenced by the specified serial correlation model. Hence, as was the case when extending the original model to correlated errors, we again would obtain sensitivity of the estimated association for the evolutions to the specified error structure.

To study the association of the evolutions, an alternative would be the two-stage approach with the discussed correction for the measurement error in the first stage. However, this approach assumes that enough information is available for each subject to obtain in the first stage estimates of the regression coefficients and standard errors for these estimates.

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