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Multivariate Generalized Linear Mixed Models With Random Intercepts To Analyze Cardiovascular Risk Markers in Type-1 Diabetic Patients

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Abstract

Statistical approaches tailored to analyzing longitudinal data that have multiple outcomes with different distributions are scarce. This paucity is due to the non-availability of multivariate distributions that jointly model outcomes with different distributions other than the multivariate normal. A plethora of research has been done on the specific combination of binary-Gaussian bivariate outcomes but a more general approach that allows other mixtures of distributions for multiple longitudinal outcomes has not been thoroughly demonstrated and examined. Here we study a multivariate generalized linear mixed models approach that jointly models multiple longitudinal outcomes with different combinations of distributions and incorporates the correlations between the various outcomes through separate yet correlated random intercepts. Every outcome is linked to the set of covariates through a proper link function that allows the incorporation and joint modelling of different distributions. A novel application was demonstrated on a cohort study of Type 1 diabetic patients to jointly model a mix of longitudinal cardiovascular outcomes and to explore for the first time the effect of glycemic control treatment, plasma prekallikrein biomarker, gender and age on cardiovascular risk factors collectively.

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Keywords

Diabetes; Joint modeling; Longitudinal outcomes; Mixed distributions; Multiple outcomes; Multivariate data; Plasma prekallikrein biomarker; Separate random intercepts; Shared random coefficient

1- Introduction

Interest to examine the joint effect of treatment and covariates on multiple outcomes is frequently encountered in biomedical research. Nonetheless, joint multivariate distributions that are flexible enough to simultaneously accommodate outcomes with different distributions are not common except for the multivariate normal [15]. To analyze data with multiple outcomes that have different distributions, two general likelihood-based approaches have been commonly used: factorization and latent variable approaches. The factorization approach is based on the idea of expressing the joint distribution as a product of the marginal distribution of one outcome and the conditional distribution of the second outcome given the first. The latent approach is based on the concept that an outcome is a manifestation of a certain latent variable and given this latent variable the observed outcome follows a certain distribution. Factorization approaches to modeling mixed outcomes, specifically discrete and continuous in the longitudinal context, were discussed in the work by Zeger and Liang [27]. Specifically they discussed the conditional Gaussian distributions for mixed binary-Gaussian time series data and proposed a general Markov model with generalized estimation equations (GEE) for estimation. The limitation of this model is that inferences could depend on the outcome that was conditioned on; in addition, it required that at least one of the outcomes should be on a binary scale while the rest should be continuous. Few studies that used the latent variable approach to analyze outcomes of different distributions exist in the literature [2, 16, 17, 21, 23]. Moreover, Bayesian latent variable models for clustered data with mixed outcomes were also developed [9]. Some of these approaches had drawbacks that were highlighted in the work by Teixeira-Pinto and Normand [24]. For instance, it was noted that the latent variable method of Sammel et al [21] is non-robust for misspecification of the covariance matrix and generates biased estimates of the parameters if the outcomes are not correlated. It was also indicated that the Bayesian method by Dunson [9] produces a non-identifiable model for binary and continuous outcomes. To overcome these drawbacks Teixeira-Pinto and Normand [24] introduced a latent based approach that constrains the parameters of the latent model proposed by Dunson [9] for identifiability but without imposing any restrictions on the correlation. A few studies also attempted joint modeling of only binary and continuous outcomes for clustered data [3, 4, 7, 11, 12, 19]. However, none of these approaches considered multiple longitudinal outcomes that arise from different distributions. Among those that considered multiple longitudinal outcomes, the main focus was on outcomes with the same distribution. For example, Coull and Agresti [5] proposed methods for modeling multivariate binomial-type responses using a vector of random effects that has a mean that is a linear function of covariates. Few studies have dealt with mixed outcomes such as the work by Rochan [20] for a mix of binary and continuous and that by Gueorguieva and Sanacora [13] for a mix of ordinal and continuous outcomes. Copula based models were also developed but they were tailored to clustered data and extension to

longitudinal setting could be challenging [8]. Hence, models that are more general and tailored to jointly model longitudinal outcomes with different distributions (for example, combination of continuous outcomes such as normal, lognormal, exponential or combination of both discrete and continuous outcomes) are not well studied. Moreover, extension to more than two outcomes has not been given specific attention. Here we aim at demonstrating the application of the multivariate generalized linear mixed models (mGLMM) with separate yet correlated random intercepts (SPRI) in a setting of multiple longitudinal outcomes with a higher dimension than just the bivariate one, and with a combination of distributions that is not just limited to normal and binary. Performance of the SPRI model was compared to the more restrictive multivariate models: shared random intercept (SHRI) and shared random intercept and slope (SHRIS), and to the separate random intercepts (RI) and separate random intercepts and slopes (RIS) using simulated and real data. The outcomes are linked to the covariates using link functions that allow the incorporation of different combination of distributions to be modeled simultaneously. While shared random effect models (SHRI and SHRIS) impose strong restriction on the correlation structure by assuming that the correlation between the longitudinal measurements of the different outcomes are all the same, SPRI model relaxes this restriction by allowing separate but correlated random intercepts. In addition, while separate analysis could result in an increase in type 1 error, multivariate joint modeling accounts for the correlation between the different outcomes and hence results in more consistent and accurate estimates and inferences.

The motivating example in this study is the analysis of multiple outcomes for cardiovascular disease among type 1 diabetic patients enrolled in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study [10,25]. These correlated outcomes that were longitudinally measured comprised hemoglobin A1c (HbA1c), total cholesterol, diastolic blood pressure (DBP), and systolic blood pressure (SBP). While the latter three had lognormal distribution, HbA1c was used as a binary outcome. Specifically, HbA1c was dichotomized to either above or below 7 mmol/mol inclusive to indicate poor or good glycemic control respectively. In this regard, a diabetic patient with HbA1c above 7 mmol/mol is considered to have poor glycemic control and in the abnormal range of HbA1c levels. Interest was primarily focused on assessing the differential effect of plasma prekallikrein (plasma PK) biomarker and that of glycemic control treatment (intensive versus conventional) on the rate of change in the levels of these cardiovascular risk markers after adjusting for other covariates such as gender, and age at DCCT study entry. The application of the SPRI model to the DCCT/EDIC cohort is of great importance given its novelty in exploring for the first time the effects of plasma PK biomarker, treatment (intensive versus conventional) and other determinants such as age at entry to the DCCT study and gender on a group of cardiovascular risk factors collectively using joint modeling of a mix of lognormal and binary distributions rather than the conventional separate analysis on each of the outcomes. This application is of clinical significance given that it provides a holistic and comprehensive insight into the effect of these factors in promoting cardiovascular outcomes in type 1 diabetic patients. The key novelty in this research relies in demonstrating and studying the mGLMM with separate random intercepts (SPRI) in the context of multiple outcomes. To our knowledge, SPRI model has been discussed in the bivariate setting only but thorough assessment of this model

in the setting of multivariate high dimensional longitudinal outcomes with any combination of mixed distributions has not been given full consideration. The term mixed or mixtures of distributions, is used in this manuscript to refer to a combination of different distributions for the multiple outcomes. Moreover, the application of this model on the DCCT/EDIC cohort of diabetic subjects has never been conducted before and assessment of the various determinants on the markers of cardiovascular complications is a key novelty.

The rest of the article is organized as follows. The multivariate generalized linear mixed models are described in Sections 2 and 3. The univariate generalized linear mixed models are detailed in Section 4. In Section 5 we discuss the results of the simulation study conducted to assess the performance of the different multivariate and univariate generalized linear mixed models in comparison to SPRI, and the application of these models on the cohort of type 1 diabetic patients is detailed in Section 6. Conclusion and discussion are included in Section 7.

2- Multivariate Generalized Linear Mixed Models (mGLMM) with Separate Random Intercepts (SPRI)

Let $Y_{ij1}, Y_{ij2}, \dots, Y_{ijk}$ be the multivariate outcomes for subject i , measured at times $j=1$ to t_i , for outcomes 1 to k . The SPRI can be described for 4 outcomes with mixed distributions as such:

$$\begin{aligned} E(Y_{ij1}|b_{0i1}) &= g_1^{-1}(\beta_{01} + b_{0i1} + \beta_{11}t_j + \beta_{21}x_i) \\ E(Y_{ij2}|b_{0i2}) &= g_2^{-1}(\beta_{02} + b_{0i2} + \beta_{12}t_j + \beta_{22}x_i) \\ E(Y_{ij3}|b_{0i3}) &= g_3^{-1}(\beta_{03} + b_{0i3} + \beta_{13}t_j + \beta_{23}x_i) \\ E(Y_{ij4}|b_{0i4}) &= g_4^{-1}(\beta_{04} + b_{0i4} + \beta_{14}t_j + \beta_{24}x_i) \end{aligned} \quad (1)$$

$$b_{0i} = \begin{pmatrix} b_{0i1} \\ b_{0i2} \\ b_{0i3} \\ b_{0i4} \end{pmatrix} \sim MVN(0, D_{4 \times 4})$$

where 10 parameters need to be estimated in the variance-covariance matrix D . These parameters are attributed to 4 variances and 6 covariances between the intercepts. The correlation between the outcomes is therefore assumed to be captured by the correlation between the separate intercepts. The correlation between the repeated measures for the same subject for outcome k is captured by the random intercept b_{0ik} . The vector of covariates of interest is denoted as x_i . The inverse link function is denoted as g_k^{-1} and is relevant to outcome k as it reflects the particular distribution of the outcome. In our diabetes example the outcomes had a mixture of lognormal and binary distributions but the model can accommodate any combination of distributions, along with any number of outcomes and covariates.

The joint marginal density for (y_1, y_2, y_3, y_4) is

$$f(y_1, y_2, y_3, y_4) = \int f(y_1, y_2, y_3, y_4|b) f(b) db = \int f(y_1|b) f(y_2|b) f(y_3|b) f(y_4|b) f(b) db \quad (2)$$

Where $f(b)$ denotes the random effects density that is assumed to be normal as previously described.

3- Other Multivariate Generalized Linear Mixed Models (mGLMM)

In addition to the SPRI model, other possibilities to link the separate Generalized Linear Mixed Models (GLMM) in the mGLMM is by having a single shared random intercept (SHRI), or shared random intercept and slope (SHRIS). These models can be described as such:

3.1 Shared Random Intercept (SHRI)

Let $Y_{ij1}, Y_{ij2}, \dots, Y_{ijk}$ be the multivariate outcomes for subject i , measured at times $j=1$ to t_i , for outcomes 1 to k . For 4 outcomes with mixed distributions, SHRI model can be described as follows:

$$\begin{aligned} E(Y_{ij1}|b_{0i}) &= g_1^{-1}(\beta_{01} + b_{0i} + \beta_{11}t_j + \beta_{21}x_i) \\ E(Y_{ij2}|b_{0i}) &= g_2^{-1}(\beta_{02} + b_{0i} + \beta_{12}t_j + \beta_{22}x_i) \\ E(Y_{ij3}|b_{0i}) &= g_3^{-1}(\beta_{03} + b_{0i} + \beta_{13}t_j + \beta_{23}x_i) \\ E(Y_{ij4}|b_{0i}) &= g_4^{-1}(\beta_{04} + b_{0i} + \beta_{14}t_j + \beta_{24}x_i) \end{aligned} \quad (3)$$

where $b_{0i} \sim MVN(0, \sigma_b^2)$, σ_b^2 is the variance for the intercept. The correlation between the outcomes is assumed to be captured by the shared-common intercept b_{0i} . In addition, the correlation between the repeated measures pertaining to the same subject for the same outcome, is also accounted for through the random effect b_{0i} .

3.2 Shared Random Intercept and Slope (SHRIS)

In this model the correlation between the outcomes is assumed to be captured by the shared-common intercept b_{0i} and slope b_{1i} . Moreover, the correlation between the repeated measures on the same individual for the same outcome is also accounted for through the

$$\text{random effect } b_i = \begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix}.$$

The SHRIS model is described as follows:

$$\begin{aligned} E(Y_{ij1}|b_i) &= g_1^{-1}(\beta_{01} + b_{0i} + (b_{1i} + \beta_{11})t_j + \beta_{21}x_i) \\ E(Y_{ij2}|b_i) &= g_2^{-1}(\beta_{02} + b_{0i} + (b_{1i} + \beta_{12})t_j + \beta_{22}x_i) \\ E(Y_{ij3}|b_i) &= g_3^{-1}(\beta_{03} + b_{0i} + (b_{1i} + \beta_{13})t_j + \beta_{23}x_i) \\ E(Y_{ij4}|b_i) &= g_4^{-1}(\beta_{04} + b_{0i} + (b_{1i} + \beta_{14})t_j + \beta_{24}x_i) \end{aligned} \quad (4)$$

$b_i = \begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} \sim MVN(0, D_{2 \times 2})$ where D is the variance-covariance matrix of the shared and slope, so intuitively it includes the variances of the intercept and slope and their covariance. Using the same random effect (or effects when the random slope is included) to

model the correlation between outcomes and the longitudinal process is not ideal since it imposes a strong restriction in the correlation structure. Specifically, models with a single random intercept or intercept and slope assume that the correlations between the longitudinal measurements of the outcomes are all the same which is an unlikely situation. However, SPRI relaxes this assumption by allowing outcomes to have separate but correlated random intercepts.

4. Univariate Generalized Linear Mixed Models (GLMM)

In the GLMMs the single outcome could be described in terms of random intercepts (RI models) or random intercepts and slopes (RIS models). Application of the univariate GLMMs on multivariate outcomes entails fitting a GLMM for each outcome separately. However, this separate analysis, could lead to wrong inferences and might result in an inflation of type 1 error due to failure to account for the correlation between the multiple outcomes.

The two univariate GLMM approaches can be specified as such:

Random Intercepts (RI)

For outcome k we assume the following model

$$\begin{aligned} E(Y_{ijk}|b_{0ik}) &= g^{-1}(\beta_{0k} + b_{0ik} + \beta_{1k}t_j + \beta_{2k}x_i) \\ b_{0ik} &\sim N(0, \sigma_{b_k}^2) \end{aligned} \quad (5)$$

Random Intercepts and Slopes (RIS)

For outcome k we assume the following model

$$E(Y_{ijk}|b_{ik}) = g^{-1}(\beta_{0k} + b_{0ik} + (b_{1ik} + \beta_{1k})t_j + \beta_{2k}x_i) \quad (6)$$

$b_{ik} = \begin{pmatrix} b_{0ik} \\ b_{1ik} \end{pmatrix} \sim N(0, D_{k \times 2})$ where D_k is the variance-covariance matrix for the intercept and slope pertaining to the outcome K.

All these models can be estimated by pseudo-likelihood techniques using PROC GLIMMIX in SAS 9.3 [22]. When the responses have different distributions, this can be handled via the DIST=BYOBS (variable) option in the MODEL statement which instructs the GLIMMIX procedure in SAS to examine the distribution and corresponding link for each outcome. Model comparison could also be facilitated using pseudo AIC, BIC and $-2\log L$ criteria.

5. Simulation Study

The mGLMM with separate random intercepts (SPRI) model was demonstrated using a simulation study in which datasets were bootstrapped from the DCCT/EDIC dataset. Estimates $\hat{\theta}$ generated under SPRI when applied on the DCCT/EDIC were compared to the

estimates $\hat{\theta}_{Boot}$ generated under SPRI when applied on the bootstrapped datasets. Specifically consistency of the estimates was assessed using the mean and mean squared of the differences between $\hat{\theta}$ and $\hat{\theta}_{Boot}$. These performance indicators can be described as such:

Mean Difference = $\frac{1}{r} \sum_{i=1}^r (\hat{\theta}_{Boot,i} - \hat{\theta})$ and Mean Squared Difference = $\frac{1}{r} \sum_{i=1}^r (\hat{\theta}_{Boot,i} - \hat{\theta})^2$ where r indicate the number of replication. Here, we conducted 500 replications each with a sample size of 569.

For the other multivariate and univariate models similar simulation study was conducted with the exception that $\hat{\theta}$ and $\hat{\theta}_{Boot}$ were estimated from the application of a particular model (for instance RI) on the DCCT/EDIC dataset and on the simulatd datasets respectively. The model that had smaller values for the performance indicators is considered to have more consistent and stable estimates in comparison to the other models. The objective of this study is to examine the performance of the mGLMM SPRI, the model of interest in this paper, in comparison to the other models that are considered less suitable for the longitudinal multivariate mixed outcomes settings and to assess whether in reality the added level of complexity embedded in the SPRI model is outweighed by the gain in its performance. Data were simulated for the binary outcome HbA1c and for total cholesterol and DBP with a lognormal distribution. The covariates of interest included square root of year of measurement, the 3 tertile groups of Plasma PK, treatment groups intensive versus control, gender, and age. Analysis was adjusted for the effect of year to account for the quadratic relationship between the outcomes and square root of year. Our results indicated that SPRI had a smaller Mean Difference (See Table 1, Column 10) in the majority of the estimates in comparison with the other multivariate models. Specifically the Mean Difference for 11 estimates out of a total of 21 under the SPRI model was smaller than the Mean Differences under SHRI (Table 1, Column 4) and SHRIS (Table 1, Column 7). If we consider the 1st tertile of Plasma PK, we notice that the Mean Differences for the 3 outcomes (Total Cholesterol, DB, and HbA1c) were the smallest under SPRI compared to the Mean Differences under SHRI and SHRIS. For instance, the Mean Difference for the 1st tertile of Plasma PK attributed to the DBP outcome was 0.049 for SPRI, but it increased to 0.432 under SHRIS and 0.732 under SHRI; thus, this suggests an increase of about 9 and 15 fold in this performance indicator respectively. With respect to the Mean Squared Difference, similar conclusion can be drawn since SPRI had the smallest values for this performance indicator in 11 out of 21 total estimates (See Table 1, Column 11) compared to the ones generated under SHRI (Table 1, Column 5) and SHRIS (Table 1, Column 8). For instance if one considers the estimate for the 1st tertile of Plasma PK generated for the Total Cholesterol outcome, it can be noted that the Mean Squared Difference increases from 0.07 under SPRI model to about 0.14 (about 2 fold increase) under SHRI and SHRIS.

When comparing SPRI to the univariate model with random intercept (RI), it can be noted that SPRI had smaller Mean Differences in 11 out of 21 estimates (See Table 1, Column 10 for SPRI and Table 2, Column 4 for RI). For instance the Mean Differences for the 1st and 2nd tertiles of Plasma PK estimates attributed to the DBP outcome were smaller under the SPRI model and had values of 0.049 and 0.026 compared to the values of 0.157 and 0.331

under the RI model. Hence the Mean Differences reported under the RI model increased by about 3.2 to 12.7 fold respectively in comparison to the SPRI model. Similar observation can be drawn for the Mean Differences for SPRI compared to RIS where the values of this performance indicator were smaller in 13 out of 21 estimates generated under SPRI (See Table 1, Column 10, and Table 2, Column 7). For instance, the Mean Difference for the 1st tertile of Plasma PK attributed to the DBP outcome was 0.049 under SPRI and it increased to 0.214 under RIS i.e. increased by about 4.4 fold. The Mean Squared Differences were smaller or about the same in SPRI compared to the univariate models. Hence the performance indicators under the mGLMM SPRI model were smaller than the other multivariate and univariate models indicating better consistency in the estimates.

6. Diabetes Application

Our study was motivated by the DCCT/EDIC cohort of type 1 diabetic subjects. The original DCCT cohort consisted of men and women between the ages of 13-40 with 1-15 years of diabetes at study entry [25]. The patients enrolled in the DCCT between 1983 and 1989 and the original randomized clinical trial ran for approximately 6.5 years. Half of the patient population was randomly assigned to conventional diabetes treatment and the other half was assigned to intensive diabetes treatment. In 1993, the DCCT study was stopped when intensive treatment was clearly shown to reduce the risks of retinopathy, nephropathy and neuropathy [26]. The patients were enrolled in EDIC, a longitudinal observational study of the development of macrovascular complications and further progression of microvascular complications [10]. Fasting plasma samples were collected from the subjects for measurements of Plasma PK and shipped from participating EDIC centers to the Medical University of South Carolina (MUSC). Exciting newly generated information implicated Plasma PK as a modulator of diabetic microvascular complications (nephropathy). In this context, we were able to show that abnormalities in Plasma PK activity are associated with increased blood pressure and greater albumin excretion rate in type 1 diabetic patients [14]. Moreover our recent findings have demonstrated a role for Plasma PK in vascular remodeling by promoting growth of vascular smooth muscle cells through transactivation of epidermal growth factor receptors [1]. Hence in this study we aim at assessing the role of Plasma PK as a risk marker for cardiovascular disease accounting for covariates such as gender and age at entry to the DCCT study. We also accounted for treatment effect at DCCT on these outcomes. Five longitudinal measures of Plasma PK were generated for 569 DCCT/EDIC type 1 diabetic patients for the period between year 1983 and 2005 and registered as year 0, year 10, year 16, year 20, and year 22. Repeated measures were also registered for total cholesterol, SBP, DBP, and HbA1c for the same period of time. The first three outcomes had a lognormal distribution while HbA1c had a binary distribution and dichotomized as above 7 mmol/mol or below it inclusive. Clinically, it is known that patients with HbA1c levels greater than 7 mmol/mol are considered to have poor glucose control and their HbA1c indicator is set to 1 for this measurement time point. However, patients with HbA1c below or equal to this cutoff point of 7 mmol/mol are considered to have controlled glucose and the HbA1c indicator at this measurement time point is set to zero.

Square root of the year was used instead of the original scale to bring the measures closer and minimize the gap between the measurement time points, but its square was also included to account for the curvilinear relationship between every outcome and square root of year.

A closer look at the data analysis results (See Table 3a) leads to the conclusion that there was a significant difference between the first and third tertiles of PK and the second and third tertiles with respect to the outcomes total cholesterol and HbA1c. For instance, patients in the first tertile had about 10% decrease in total cholesterol compared to those in the third tertile as evidenced in the SPRI model and the other multivariate models (Table 3a). Similar conclusions can be drawn for the second and third PK tertiles. Along the same line, one can also deduce that patients in the first PK tertile had decreased odds by 2.2 of having HbA1c above 7 mmol/mol compared to those in the third tertile of PK, and a decreased odds by 2 for those in the second tertile compared to third (Table 3a). These results were also supported by the mean plots that depicted the mean values for each outcome separately over square root of the measurement year and stratified by the PK tertiles (Figure 1a-d). In Figure 1a it was obvious that diabetic patients who had PK levels in the upper third tertile had higher total cholesterol levels compared to those in the lower tertiles, and so was the case for all the other 3 outcomes (see Figure 1b, 1c and 1d). Therefore, one can deduce that PK is a risk factor for cardiovascular diseases and an increase in its levels results in an associated increase in the levels of some of the outcomes for cardiovascular diseases. Treatment was shown to have a significant effect on HbA1c wherein patients who were randomized to the intensive treatment in the DCCT study appeared to exhibit decreased odds of having HbA1c above 7 mmol/mol. This conclusion was demonstrated in our model of interest SPRI, and in the other multivariate models as well as in the mean plots for these outcomes (Figure 2d). Specifically, Figure 2d reveals that patients on intensive treatment had significantly lower mean levels of HbA1c on the second, third and fourth measurements. In terms of model fitting, SPRI was the best model that fits the diabetes dataset and its associated AIC of 1238.56, BIC of 1299.38 and -2Res_Log_L of 1210.56 were the smallest compared to those under SHRI and SHRIS (Table 3b). When the univariate models were applied, similar conclusions were reached as in the multivariate setting except for DBP wherein RI suggests that there is a significant difference in this outcome between the first and third tertiles of PK (Table 4) suggesting a possible type 1 error. With respect to gender, it appeared to be consistently significantly associated with SBP and DBP across all models (P-value < 0.0001) with females having a decreased blood pressure of about 5% compared to males. A significant association between gender and total cholesterol as well as HbA1c (P-value = 0.02) was detected in SHRI and SHRIS models. In this respect, females appeared to have an increase of 2% in total cholesterol and decreased odds of 1.2 times in having HbA1c above 7 mmol/mol compared to males. However, this association was detected only in the shared effects models and not in the model of interest SPRI. This could suggest inflation in type1 error in the shared random effects models.

Age exhibited a consistent significant association with SBP and total cholesterol (P-value < 0.05) in all models and those who were above the age 27 years had between 2 and 4% increase in these outcomes compared to those who were younger than this age. A significant association was observed between age and HbA1c only in the SHRI and SHRIS models (P-value = 0.014) with increased odds of 1.2 times of having HbA1c above 7 mmol/mol for

those whose ages were above 27 years compared to those below this age. However, this association was not detected under the SPRI model.

The standard errors generated under the SPRI model were smaller than those under its univariate counterpart RI. Specifically, 16 estimates out of 28 had smaller SEs under this multivariate model SPRI (See Table 3) compared to its univariate counterpart RI (See Table 4). The remaining estimates had about the same SEs in both models or slightly smaller under RI. Estimates for treatment effect were about the same between SPRI and RI; however, estimates for PK tertiles had smaller SE under SPRI compared to RI for all outcomes except for total cholesterol.

It is important to highlight here that the variance-covariance matrix for SPRI had 14 parameters to be estimated compared to a total of 5 parameters under SHRI, and 2 parameters for every outcome under the RI model (See Appendix 1 and Appendix 2). In spite of this increased number of parameters under SPRI, this model still generated estimates with smaller SEs compared to the simple univariate model RI. However this large number of parameters could explain the inconsistency in observing reduction in SEs in SPRI compared to SHRI. Hence multivariate modeling with separate random effects generates estimates with overall smaller SEs than the univariate counterparts and clearly was the best fit for the diabetes dataset.

7. Conclusion

In this paper we demonstrated how to jointly model multiple longitudinal outcomes with mixed distributions using multivariate generalized linear mixed models (mGLMM) with separate random intercepts (SPRI). To our knowledge, this model was primarily demonstrated in the context of 2 outcomes only and with distributions that are mainly limited to binary and continuous. Here we studied this model in the context of multiple outcomes measured longitudinally and expanded the mixtures of distributions to any combination.

Every outcome in the mGLMM SPRI model is related to the covariates through a link function that is relevant to its distribution. The interdependency between the multiple outcomes and the longitudinal nature of the data were accounted for through the separate yet correlated random intercepts. Using common random effects as in SHRI and SHRI-S to model the correlation between the outcomes and the longitudinal process imposes a strong restriction in the correlation structure since it assumes that the correlations between the longitudinal measurements of the multiple outcomes are all the same. However, by having separate random intercepts as in SPRI relaxes this restriction. Our simulation results showed that SPRI had the best consistency in the majority of the estimates compared to the other multivariate and univariate generalized linear mixed models. Hence, the improved performance of the SPRI model compensates for its added level of complexity. The more advanced model that incorporates separate random intercepts and slopes (SPRIS) had convergence issues with the mixed distributions and was not considered here. Nonetheless, in an unpublished work we showed that SPRI had the best performance compared to SPRIS when modeling Gaussian multivariate longitudinal outcomes. We anticipate that this

conclusion will be also applicable in the context of multiple outcomes with mixed distributions.

A novel clinical application of the SPRI model on the DCCT/EDIC cohort was also presented here. This application is of great clinical significance since it provides a combined assessment of the differential effects of the biomarker plasma PK, treatment and other covariates on the cardiovascular disease outcomes that have different distributions using joint modeling rather than the conventional separate analysis conducted on each outcome alone which typically results in an inflated type 1 error in the inferences about the estimates.

The advantage of the mGLMM SPRI model is its feasibility of implementation using a standard software package such as SAS PROC GLIMMIX. Moreover, this model does not require the assumption that one outcome is of less interest than the other and hence can be conditioned over as stipulated in the location model [18] or Cox's model [6]. In addition, we demonstrated here the feasibility of this model to handle mixed outcomes with high dimension and successful convergence was consistently achieved, unlike the location model [18] or Cox's model [6]. Furthermore, additional advantage of the SPRI model is embedded in its flexibility to incorporate several covariates and to accommodate longitudinal and clustered data with high dimensional outcomes that have different distributions not only limited to the binary-Gaussian combination. Hence, we conclude that the computational feasibility to accommodate longitudinal outcomes of high dimension and with mixed distributions is a key feature of the SPRI model.

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Appendix 1

Variance-Covariance matrix of SHRI and SHRIS when applied on the diabetes dataset with mixed outcomes

Model	Outcome	Variance Intercept (SE)	Covariance Intercept, Slope (SE)	Variance Slope (SE)	Variance Residuals (SE)
SHRI		0.00292 (0.00023)			
	Total Cholesterol				0.02787 (0.00081)
	SBP				0.00889 (0.00026)
	DBP				0.00989 (0.00029)
	HbA1c				1.00400 (0.02667)
SHRIS		0.00349 (0.00043)	-0.00033 (0.000089)	0.00015 (0.00002)	

Variance-Covariance matrix of SHRI and SHRIS when applied on the diabetes dataset with mixed outcomes

Model	Outcome	Variance Intercept (SE)	Covariance Intercept, Slope (SE)	Variance Slope (SE)	Variance Residuals (SE)
	Total Cholesterol				0.02801 (0.00082)
	SBP				0.00836 (0.00025)
	DBP				0.00921 (0.00028)
	HbA1c				1.00400 (0.02667)

Variance-Covariance matrix of SPRI when applied on diabetes dataset with mixed outcomes

Outcome	Variance Intercept (SE)	Covariance intercepts Total Chol, SBP (SE)	Covariance intercepts Total Chol, DBP (SE)	Covariance intercepts Total Chol, HbA1c (SE)	Covariance intercepts SBP, DBP (SE)	Covariance intercepts SBP, HbA1c (SE)	Covariance intercepts DBP, HbA1c (SE)	Variance Residuals (SE)
SPRI	0.01738 (0.001121)	0.00114 (0.000042)	0.00120 (0.000044)	0.04875 (0.01117)	0.00321 (0.000025)	0.01178 (0.000531)	0.00541 (0.000556)	0.01378 (0.00042)
SBP	0.00300 (0.000029)							0.00863 (0.00026)
DBP	0.00341 (0.000033)							0.00949 (0.00028)
HbA1c	2.21820 (0.21590)							0.75170 (0.02272)

Appendix 2

Variance-Covariance matrix of RI and RIS when applied on diabetes dataset

Model	Outcome	Variance Intercept (SE)	Covariance Intercept, Slope (SE)	Variance Slope (SE)	Variance Residuals (SE)
RI	Total Cholesterol	0.01725 (0.001197)			0.01383 (0.000420)
	SBP	0.002899 (0.000282)			0.008691 (0.000263)
	DBP	0.003288 (0.000316)			0.009563 (0.000290)
	HbA1c	1.5709 (0.1720)			(---) (---)
RIS	Total Cholesterol	0.02015 (0.001926)	-0.00108 (0.000322)	0.000421 (0.000079)	0.01226 (0.000447)
	SBP	0.000790 (0.000615)	0.000376 (0.000170)	0.000218 (0.000098)	0.008736 (0.000308)
	DBP	0.005900 (0.000880)	-0.00073 (0.000193)	0.000216 (0.000053)	0.008759 (0.000309)
	HbA1c	0.4625 (0.1288)	0.2437 (0.03568)	<0.0001 <0.0001	(---) (---)

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(a)

(b)

(c)

(d)

Figure 1.

Mean plots showing the mean values for a) Total Cholesterol b) SBP c) DBP d) HbA1c over square root of the measurement year and stratified by the Plasma Prekallikrein (PK) tertiles.

Figure 2.

Mean plots showing the mean values for a) Total Cholesterol b) SBP c) DBP d) HbA1c over square root of the measurement year and stratified by the treatment groups.

Table 1

Simulation Study Results on SPRI and the Other Multivariate Models: Replicate 500 and Sample size 569

SHRI			SHRIS			SPRI		
Performance Indicators			Performance Indicators			Performance Indicators		
Estimate	Outcome	$\hat{\theta}$	Mean Difference	Mean Squared Difference	$\hat{\theta}$	Mean Difference	Mean Squared Difference	$\hat{\theta}$
Intercept	$\bar{F}_{Total\ Cholesterol*100}$	5.14310	-0.07155	0.02492	5.14230	-0.10657	0.02699	5.12760
	DBP*1000	4.31410	-0.96538	0.07737	4.31330	-0.62663	0.13349	4.31740
	HbA1c	2.08230	0.02076	0.04045	2.08120	0.03222	0.04002	2.41790
Year_SQRT	$\bar{F}_{Total\ Cholesterol*1000}$	0.04321	0.00478	0.02963	0.04318	0.33142	0.02602	0.03940
	DBP*1000	0.02424	-0.49164	0.02446	0.02423	-0.41584	0.02201	0.02506
	HbA1c	-0.40780	0.00316	0.00831	-0.40790	0.00458	0.00793	-0.60040
Plasma PK 1st tertile	$\bar{F}_{Total\ Cholesterol*1000}$	-0.06665	0.15948	0.13962	-0.06645	-0.60679	0.13809	-0.04593
	DBP*1000	-0.00671	0.73248	0.04373	-0.00648	-0.43203	0.03610	-0.01082
	HbA1c	-0.79800	-0.00789	0.01858	-0.79770	-0.02281	0.01749	-0.66580
Plasma PK 2nd tertile	$\bar{F}_{Total\ Cholesterol*1000}$	-0.03722	-0.16940	0.08726	-0.03683	-0.75899	0.08299	-0.02331
	DBP*100	-0.01232	0.00056	0.00338	-0.01190	-0.11735	0.00351	-0.01522
	HbA1c	-0.44520	-0.00790	0.01583	-0.44480	-0.00863	0.01636	-0.36360
Gender	$\bar{F}_{Total\ Cholesterol*1000}$	0.01753	-0.01370	0.15157	0.01802	0.39839	0.20458	0.01756
	DBP*1000	-0.05048	0.09275	0.03755	-0.04999	0.88884	0.11192	-0.05057
	HbA1c	-0.18110	-0.01223	0.01395	-0.18050	-0.01242	0.01530	-0.20800
Age	$\bar{F}_{Total\ Cholesterol*1000}$	0.04085	-0.24350	0.16095	0.04168	0.28536	0.17956	0.04247
	DBP*1000	0.00661	0.42713	0.03450	0.00745	0.94506	0.06740	0.00636
	HbA1c	0.19880	0.00653	0.01364	0.19970	0.01788	0.01399	0.25830
Treatment Group	$\bar{F}_{Total\ Cholesterol*100}$	0.02582	0.11767	0.01633	0.02577	0.11262	0.01753	0.02583
	DBP*1000	-0.00362	0.03280	0.03921	-0.00369	-0.11665	0.03947	-0.00362
	HbA1c	-0.28510	-0.00335	0.01685	-0.28520	-0.01381	0.01782	-0.28510

$\bar{F}$ Performance Indicator should be multiplied by the number specified next to the outcome name

Table 2

Simulation Study Results on the Univariate Models; Replicate 500 and Sample size 569

Estimate	Outcome	RI			RIS		
		Performance Indicators			Performance Indicators		
		$\hat{\theta}$	Mean Difference	Mean Squared Difference	$\hat{\theta}$	Mean Difference	Mean Squared Difference
Intercept	$\mathcal{F}_{\text{Total Cholesterol}}*100$	5.12900	-0.05635	0.02183	5.12020	-0.04565	0.02255
	DBP*1000	4.31840	-0.35644	0.07403	4.31740	-0.38290	0.07449
	HbA1c	2.29900	0.01986	0.05361	2.08300	0.02485	0.05074
Year_SQRT	$\mathcal{F}_{\text{Total Cholesterol}}*1000$	0.03986	0.08616	0.02462	0.03832	0.11656	0.02424
	DBP*1000	0.02536	-0.37888	0.02452	0.02517	-0.36636	0.02418
	HbA1c	-0.52740	0.00466	0.01205	-0.44200	0.00345	0.01192
Plasma PK 1st tertile	$\mathcal{F}_{\text{Total Cholesterol}}*1000$	-0.04802	0.05109	0.06825	-0.03947	-0.08443	0.07240
	DBP*1000	-0.01227	-0.15715	0.03555	-0.01097	-0.21416	0.03440
	HbA1c	-0.72330	-0.00743	0.02138	-0.71730	-0.01136	0.02307
Plasma PK 2nd tertile	$\mathcal{F}_{\text{Total Cholesterol}}*1000$	-0.02423	-0.18798	0.04348	-0.01862	-0.27241	0.04342
	DBP*1000	-0.01600	-0.33164	0.02942	-0.01490	-0.32575	0.03018
	HbA1c	-0.39820	-0.01050	0.01764	-0.37730	-0.00944	0.01877
Gender	$\mathcal{F}_{\text{Total Cholesterol}}*1000$	0.01740	-0.06415	0.15034	0.02108	-0.07186	0.15698
	DBP*1000	-0.05063	0.08034	0.03748	-0.05054	0.09958	0.03741
	HbA1c	-0.20220	-0.01184	0.01863	-0.09590	-0.01426	0.01870
Age	$\mathcal{F}_{\text{Total Cholesterol}}*1000$	0.04252	-0.28484	0.16090	0.04447	-0.34654	0.16365
	DBP*1000	0.00631	0.40837	0.03433	0.00622	0.33992	0.03441
	HbA1c	0.23420	0.00735	0.01798	0.10900	0.00646	0.01755
Treatment Group	$\mathcal{F}_{\text{Total Cholesterol}}*100$	0.02500	0.11987	0.01623	0.02506	0.11509	0.01602
	DBP*1000	-0.00370	0.02487	0.03885	-0.00361	0.03031	0.03904
	HbA1c	-0.34240	-0.00217	0.02232	-0.33800	0.00061	0.02116

 $\mathcal{F}$ Performance Indicator should be multiplied by the number specified next to the outcome name

Table 3a
Application of the 4 multivariate models on the diabetes dataset with outcomes having mixed distributions

Model	Outcome	Intercept (SE)	P-value	Slope sqrt Year (SE)	P-value	Slope Plasma PK 1st tertile (SE)	P-value	Slope Plasma PK 2nd tertile (SE)	P-value	Slope Female (SE)	P-value	Slope Age > 27 (SE)	P-value	Treatment group (SE)	P-value
SHRI	Total Cholesterol	5.14170		0.04287		-0.07000		-0.04000		0.01764		0.04070		0.02566	
		(0.01193)		(0.00826)		(0.00872)		(0.00843)		(0.00788)		(0.00783)		(0.00782)	
		<0.0001		<0.0001		<0.0001		<0.0001		0.0251		<0.0001		0.0010	
SBP	SBP	4.74930		0.05627		0.00268		-0.00256		-0.04812		0.02535		-0.00719	
		(0.00780)		(0.00468)		(0.00535)		(0.00501)		(0.00582)		(0.00578)		(0.00578)	
		<0.0001		<0.0001		0.6162		0.6095		<0.0001		<0.0001		0.2136	
DBP	DBP	4.31250		0.02397		-0.00436		-0.01103		-0.05037		0.00700		-0.00363	
		(0.00807)		(0.00493)		(0.00557)		(0.00524)		(0.00594)		(0.00591)		(0.00590)	
		<0.0001		<0.0001		0.4342		0.0354		<0.0001		0.2715		0.5381	
HbA1c	HbA1c	2.08040		-0.40830		-0.79550		-0.44410		-0.18080		0.19900		-0.28510	
		(0.15440)		(0.10510)		(0.10760)		(0.10620)		(0.08178)		(0.08154)		(0.08139)	
		<0.0001		0.0001		<0.0001		<0.0001		0.0270		0.0147		0.0005	
SHRIS	Total Cholesterol	5.13920		0.04247		-0.06193		-0.03393		0.01793		0.04151		0.02565	
		(0.01204)		(0.00830)		(0.00883)		(0.00855)		(0.00789)		(0.00784)		(0.00783)	
		<0.0001		<0.0001		<0.0001		<0.0001		0.0231		<0.0001		0.0011	
SBP	SBP	4.74690		0.05587		0.00512		-0.00100		-0.04784		0.02615		-0.00716	
		(0.00779)		(0.00457)		(0.00538)		(0.00505)		(0.00575)		(0.00572)		(0.00571)	
		<0.0001		<0.0001		0.3409		0.9218		<0.0001		<0.0001		0.2094	
DBP	DBP	4.31000		0.02358		-0.00189		-0.00892		-0.05008		0.00732		-0.00361	
		(0.008023)		(0.00479)		(0.00557)		(0.00525)		(0.00585)		(0.00582)		(0.00581)	
		<0.0001		<0.0001		0.7349		0.0893		<0.0001		0.2089		0.5342	
HbA1c	HbA1c	2.07750		-0.40880		-0.79270		-0.44190		-0.18060		0.2000		-0.28520	
		(0.15440)		(0.10510)		(0.10760)		(0.10620)		(0.08178)		(0.08154)		(0.08139)	
		<0.0001		0.0001		<0.0001		<0.0001		0.0273		0.0142		0.0005	

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Model	Outcome	Intercept (SE) P-value	Slope sqrt Year (SE) P-value	Slope Plasma PK 1st tertile (SE) P-value	Slope Plasma PK 2nd tertile (SE) P-value	Slope Female (SE) P-value	Slope Age > 27 (SE) P-value	Treatment group (SE) P-value
SPRI	Total Cholesterol	5.1273 (0.01378)	0.03933 (0.00591)	-0.04551 (0.00793)	-0.02308 (0.00699)	0.01757 (0.01201)	0.04247 (0.01196)	0.02505 (0.01195)
		<0.0001	<0.0001	<0.0001	0.0010	0.1437	0.0004	0.0361
SBP	SBP	4.75060 (0.00777)	0.05661 (0.00461)	0.00107 (0.00531)	-0.00383 (0.00496)	-0.04812 (0.00583)	0.02523 (0.00581)	-0.00719 (0.00579)
		<0.0001	<0.0001	0.8406	0.4399	<0.0001	<0.0001	0.2151
DBP	DBP	4.31370 (0.00821)	0.02424 (0.00483)	-0.00571 (0.00559)	-0.01224 (0.00521)	-0.05039 (0.00618)	0.00636 (0.00615)	-0.00369 (0.00614)
		<0.0001	<0.0001	0.3075	0.0189	<0.0001	0.3014	0.5481
HbA1c	HbA1c	2.40870 (0.20590)	-0.60370 (0.10610)	-0.65200 (0.13480)	-0.35570 (0.12240)	-0.20660 (0.15230)	0.25900 (0.15190)	-0.37220 (0.15160)
		<0.0001	<0.0001	<0.0001	0.0037	0.1748	0.0883	0.0141

Table 3b

Measures of fit for the multivariate models applied on diabetes dataset with mixed outcomes

Model	AIC	BIC	−2 Res_Log_L
SHRI	1355.66	1377.38	1345.66
SHRIS	1288.89	1319.3	1274.89
SPRI	1238.56	1299.38	1210.56

Table 4

Application of the 2 univariate models on the diabetes dataset with mixed outcomes

Model	Outcome	Intercept (SE)	P-value	Slope Sqrt Year (SE)	P-value	Slope Plasma PK 1st tertile (SE)	P-value	Slope Plasma PK 2nd tertile (SE)	P-value	Slope Female (SE)	P-value	Slope Age > 27 (SE)	P-value	Slope Treatment Group (SE)	P-value
RI	Total Cholesterol	5.12900		0.03986		-0.04802		-0.02423		0.01740		0.04252		0.02500	
		(0.01377)		(0.00592)		(0.00797)		(0.00701)		(0.01198)		(0.01193)		(0.01191)	
		<0.0001		<0.0001		<0.0001		0.0006		0.1465		0.0004		0.0360	
SBP	SBP	4.75240		0.05762		-0.00224		-0.00403		-0.04835		0.02523		-0.00715	
		(0.00787)		(0.00464)		(0.00562)		(0.00517)		(0.00578)		(0.00575)		(0.00574)	
		<0.0001		<0.0001		0.6906		0.4358		<0.0001		<0.0001		0.2135	
DBP	DBP	4.31840		0.02536		-0.01227		-0.01600		-0.05063		0.00631		-0.00370	
		(0.00830)		(0.00487)		(0.00591)		(0.00544)		(0.00612)		(0.00609)		(0.00608)	
		<0.0001		<0.0001		0.0380		0.0033		<0.0001		0.3002		0.5435	
HbA1c	HbA1c	2.29900		-0.5274		-0.7233		-0.39820		-0.2022		0.23420		-0.34240	
		(0.20620)		(0.11610)		(0.14150)		(0.13080)		(0.13980)		(0.13950)		(0.13920)	
		<0.0001		<0.0001		<0.0001		0.0024		0.1482		0.0933		0.0140	
RIS	Total Cholesterol	5.12020		0.03832		-0.03947		-0.01862		0.02108		0.04447		0.02506	
		(0.01385)		(0.00567)		(0.00796)		(0.00704)		(0.01196)		(0.01191)		(0.01189)	
		<0.0001		<0.0001		<0.0001		0.0082		0.0780		0.0002		0.0352	
SBP	SBP	4.75270		0.05662		0.002365		-0.00093		-0.05270		0.02150		-0.00699	
		(0.00825)		(0.00471)		(0.00601)		(0.00558)		(0.00649)		(0.00645)		(0.00645)	
		<0.0001		<0.0001		0.6942		0.8675		<0.0001		0.0009		0.2781	
DBP	DBP	4.31740		0.02517		-0.01097		-0.01490		-0.05054		0.00622		-0.00361	
		(0.00849)		(0.00471)		(0.00591)		(0.00545)		(0.00612)		(0.00609)		(0.00608)	
		<0.0001		<0.0001		0.0636		0.0063		<0.0001		0.3073		0.5525	
HbA1c	HbA1c	2.08300		-0.4420		-0.7173		-0.37730		-0.09590		0.10900		-0.33800	
		(0.19950)		(0.11590)		(0.14670)		(0.13850)		(0.13680)		(0.13620)		(0.13600)	
		<0.0001		0.0001		<0.0001		0.0065		0.4834		0.4235		0.0130	