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A joint overdispersed marginalized random-effects model for analyzing two or more longitudinal ordinal responses

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Abstract

Disease severity is a latent concept which should be observed using a measurement tool; it can be useful in assessing disease status both cross-sectionally and longitudinally. Medsger scale is a valid instrument for assessing the systemic sclerosis severity in which the items are categorized from 0 (normal) to 4 (endstage) for each organ system. We simultaneously analyzed two of the Medsger scale items, namely, general system and skin system as two correlated ordinal responses using an overdispersed marginalized random-effects model for longitudinal ordinal data exhibiting an overdispersion pattern. In general, a random-effects approach is implemented to account for the correlation between these two stochastic processes and to make simultaneous inference; our model also accounts for temporal correlations amongst observations taken on the same subject. Another important aspect of our model is its capacity to handle data overdispersion in order to make reliable inference. Last but not least, it is proved that certain parameters in our joint model have marginal interpretations. We investigate the statistical properties of our estimators through extensive simulation study. Finally, the methodology is applied to a data of systemic sclerosis patients.

Keywords

Beta distribution, joint modeling, longitudinal ordinal outcomes, marginalized framework, overdispersion

1 Introduction

Collecting data from the same subject over time results in longitudinal data. These repeated measurements are not independent and the corresponding correlation must be taken into account to make accurate inferences. Marginal regression (i.e., generalized estimating equations) frameworks[1] and subject-specific models like generalized linear mixed models[2–4] are two main methods which have received extensive attention for longitudinal outcomes based on extending the generalized linear models.[5,6]

More recently, likelihood-based marginalized random-effects models have been introduced for categorical data. This approach was originally introduced for binary data[7,8] and after that developed for ordinal[9,10] and count[11,12] outcomes. In this approach, a marginal model is used for modeling the population averaged response as a function of covariates, and a random-effects model is used for modeling the within-subject association. Therefore, both a population averaged and subject-specific interpretations can be made by fitting just one model instead of two separate models. This approach also enables us to take advantages of likelihood-based inference, such as the availability of expression for a full-joint distribution of the observations and relaxing the missing, completely at random assumption of GEE methods in case of incomplete data.

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Overdispersion is another practical issue in categorical longitudinal data. Although random effects also capture some amount of data dispersion, single parameter distributions often do not fit data well and model extensions or more convoluted parameterization may be needed to capture all sources of variability.[3] Recently, there has been a number of attempts to capture the overdispersion in hierarchical categorical data.[13–18] One of the extensions is a so-called combined model which introduces an additional random variable with specific distribution in a random-effects model. This approach is originally introduced for univariate longitudinal binary and count outcomes[17,18] and subsequently extended for an ordinal outcome.[19] Joint modeling is a natural way of analyzing two or more responses on the same individual that are observed in certain applications. It is an effective approach which provides statistically unbiased inferences and answers to research questions that take multiple outcomes simultaneously into account.

The motivation behind this work comes from our attempt to analyze a dataset of systemic sclerosis (SSc) patients and their disease severity based on the general system (GS) and skin system (SS) scores which are ordered categorical outcomes. Two response variables, namely, GS and SS, were recorded simultaneously and longitudinally for each SSc patient and categorized based on the Medsger severity scale,[20] which we return to in Section 4. On the other hand, one of the response variables in our dataset also exhibits overdispersion which should be considered in methodology to ensure reliable inferences. However, to the best of our knowledge, currently there is no published paper dealing with overdispersion in multivariate longitudinal ordinal data using likelihood-based approaches. Thus, we propose a novel methodology that incorporates overdispersion along with joint marginalized modeling of two or more longitudinal ordinal responses extending various aspects of earlier works.[7,19] In order to draw inference from our model, we use approximate maximum likelihood estimation with the Gaussian–Hermite quadrature method since there is no closed-form of the likelihood function.

The rest of the paper is arranged as follows. In Section 2, we first introduce an overdispersed marginalized random-effects (OMRE) model for a single longitudinal ordinal response followed by an extensions of the OMRE model, called a joint overdispersed marginalized random-effects (JOMRE) model, to handle two or more longitudinal ordinal responses. This section ends with the description of maximum likelihood estimation for our models. In Section 3, we investigate the statistical properties of our estimators through a simulation study and also compare the proposed model with the joint marginalized random-effects model (JMRE) without an overdispersion component. In Section 4, the methodology is applied to a real data of systemic sclerosis patients. The paper ends with our conclusions in Section 5.

2 Methods

In this section, we describe our model to handle two or more overdispersed longitudinal ordinal responses. A marginalized random-effects model is composed of two parts: a marginal and a random-effects model. The marginal model is a function of covariates and all underlying parameters are fixed and have population averaged interpretation. The random-effects part is a subject-specific model as a function of both the fixed and random terms and a connector which relates marginal and random-effects parts. The connector is a function of the marginal model parameters and variance components of the random-effects model. Using the ‘‘combined framework,’’ one can also capture the overdispersion in longitudinal categorical data. For analyzing binary and ordinal responses using a combined model, a beta-distributed random variable (which assumes to be independent of the normal random term) is added to the random-effects part of the model.

First, we introduce an OMRE model for analyzing longitudinal ordinal data which consists of a marginal model and overdispersed random-effects model, as stated before. In the marginal part of the model, a logit link is utilized to connect marginal mean responses with covariates and a probit link is also used in the random-effects part to model the random intercepts, connector, and overdispersion.

2.1 A univariate overdispersed model for longitudinal ordinal response

Assume that Y_{ij} indicates the ordinal response variable for ith subject at jth time of measurement ($i = 1, 2, \ldots, N$ and $j = 1, 2, \ldots, n_i$). Also assume that Y_{ij} takes values in R ordered categories where a typical value is denoted by $r = 1, 2, \ldots, R$, for simplicity. The response data for the ith subject can be written as an $n_i \times 1$ vector $\boldsymbol{Y}_i^T = (Y_{i1}, \ldots, Y_{in_i})$. Let $\boldsymbol{x}_{ij}^T = (x_{ij1}, \ldots, x_{ijp})$ indicate the $p \times 1$ vector of covariate for ith subject at jth time. To handle overdispersion, we include a random variable θ in the random-effects part of the model, where we assume that θ has a beta distribution with parameters α and γ. Also, a normal random variable $b_i \sim N(0, s^2)$ is used to capture the within-subject association. These two random variables (θ and b_i) are assumed to be independent. Now, the OMRE model for a longitudinal ordinal response can be written as:

$$\begin{aligned} &Marginal\ \ model: \qquad F_{ijr} = P\left(Y_{ij} \le r \middle| \boldsymbol{x_{ij}}\right) = expit\left(\alpha_{0r} + \boldsymbol{x_{ij}^T}\beta\right) \\ &Overdispersed\ \ Random-Effects\ \ model: \qquad F_{ijr} = (b_i,\, \theta) = P\left(Y_{ij} \le r \middle| \boldsymbol{x_{ij}},\, b_i,\, \theta\right) = \theta\ \Phi\left(\Delta_{ijr} + b_i\right) \end{aligned} \tag{1}$$

where $expit(\omega) = \exp(1 + \omega^{-1})^{-1}$. Here, α_{0r} and Δ_{ijr} are intercepts, β is a $p \times 1$ vector of fixed-effects parameters and Φ is the standard normal cumulative distribution function. We assume that the α_{0r} is strictly monotonic in r which is needed for modeling a cumulative probability distribution function when $\boldsymbol{x_{ij}} = 0$. It turns out that the other set of intercepts Δ_{ijr} automatically inherits this property as shown by the following result whose proof is given in Appendix 1.

Theorem 1. In the OMRE model in equation (1), if $\alpha_{01} < \alpha_{02} < \cdots < \alpha_{0R-1}$, then $\Delta_{ij1} < \Delta_{ij2} < \cdots < \Delta_{ijR-1}$.

The intercept, Δ_{ijr}, connects the marginal and overdispersed random-effects models and can be calculated from the relationship between the marginal and conditional probabilities as follows:

$$\begin{aligned} F_{ijr} &= \int_b F_{ijr}(b_i)\, f(b_i)\mathrm{d}b_i, \\ &= \int_b \int_\theta F_{ijr}(b_i, \theta)\, p(\theta)\, f(b_i)\mathrm{d}\theta\, \mathrm{d}b_i \end{aligned} \tag{2}$$

where $f(.)$ is the probability density function of random effects which are assumed to follow a univariate normal distribution and $p(.)$ is the probability density function of a beta distribution with parameters α and γ. The closed-form of Δ_{ijr} is

$$\Delta_{ijr} = \Phi^{-1}\left\{{}^{1}\!\big/_{E(\theta)}\ expit(\alpha_{0r} + \boldsymbol{x_{ij}^T\beta})\right\} \times \left\{\sqrt{1+s^2}\right\} \tag{3}$$

see Appendix 2 for a proof. The expression shows that Δ_{ijr} depends on the fixed-effects parameter $\boldsymbol{\beta}$ and the variance components s^2 and $E(\theta) = \alpha/(\alpha+\gamma)$; more computational details for Δ_{ijr} are presented in Appendix 2. In the sequel, we assume $\alpha = e^v\gamma$ to avoid over-parameterization in the proposed model. In this case, $E(\theta) = expit(v)$ and thus, v is the only overdispersion parameter in the likelihood function in the OMRE model.

2.2 A joint overdispersed model for two or more longitudinal ordinal responses

In this section, we extend the previously proposed model (the OMRE model in Section 2.1) to accommodate two or more longitudinal ordinal responses. Consider K ($\geq$2 potentially correlated) responses observed on the same subject at the same time points denoted by $Y_{ij}^{(k)}, (k = 1, \ldots, K)$ for subject i at time j. We will use the same notations as in Section 2.1 along with the superscript(k) to index the response. We specify the marginal part of the JOMRE model as before:

$$F_{ijr}^{(k)} = P\left(Y_{ij}^{(\mathrm{k})} \le r \middle| \boldsymbol{x_{ij}}\right) = expit\left(\alpha_{0r}^{(k)} + \boldsymbol{x_{ij}^T\beta^{(k)}}\right), \quad k = 1, \ldots, K \tag{4}$$

where $\alpha_{0r}^{(k)}$ $(k = 1, \ldots, K)$ are intercepts and $\boldsymbol{\beta^{(k)}}$ are vectors of fixed-effects parameters. Next, the overdispersed random-effects model can be described as:

$$F_{ijr}^{(k)}\left(b_i^{(k)}, \theta^{(k)}\right) = P\left(Y_{ij}^{(\mathrm{k})} \le r \middle| \boldsymbol{x_{ij}}, b_i^{(k)}, \theta^{(k)}\right) = \theta^{(k)}\varphi\left(\Delta_{ijr}^{(k)} + b_i^{(k)}\right), \quad k = 1, \ldots, K \tag{5}$$

where we correlate the normally distributed random effects for all responses by assuming

$$\boldsymbol{b_i^T} = \left(b_i^{(1)}, \ldots, b_i^{(K)}\right) \sim N\left(0, \begin{bmatrix} s_1^2 & \cdots & s_{1K} \\ \vdots & \ddots & \vdots \\ s_{K1} & \cdots & s_K^2 \end{bmatrix}\right) \tag{6}$$

We also assume that response variables are conditionally independent given the normal random effects. By specifying different but correlated normal random effects for each model and considering the conditional independence assumption, we capture the correlation between responses by what is known as the random-effects approach for joint modeling. For later use in the simulation section, we note that assuming uncorrelated random effects ($s_{kl} = 0, k \neq l$)is equivalent to the independence model which analyzes each outcome separately using the OMRE model.

Overdispersion parameters $\theta^{(k)}$ are considered independent with separate beta distributions $p(\theta^{(k)}) = Beta\left(\alpha^{(k)}, \gamma^{(k)}\right)$ for $k = 1, \ldots, K$, and the same type of constraint as in the univariate case ($\alpha^{(k)} = e^{\nu^{(k)}}\gamma^{(k)}$ for $k = 1, \ldots, K$). Using this constraint, the expectation of $\theta^{(k)}$ is equal to $expit(\nu^{(k)})$. Thus, $\boldsymbol{\nu} = (\nu^{(1)}, \ldots, \nu^{(K)})$ are overdispersion parameters which are included in the likelihood function. Moreover, $\Delta = (\Delta_{ijr}^{(1)}, \ldots, \Delta_{ijr}^{(K)})$ are intercepts which can be computed using the equations (2) and (3) for each response as:

$$\Delta_{ijr}^{(k)} = \Phi^{-1}\left\{{}^{1}\!\big/ E\left(\theta^{(k)}\right)\, expit(\alpha_{0r}^{(k)} + \boldsymbol{x_{ij}^T \beta^{(k)}})\right\} \times \left\{\sqrt{1 + s_k^2}\right\}, \quad k = 1, \ldots, K. \tag{7}$$

As before, we assume that each set of intercepts ($\alpha_{0r}^{(k)}, k = 1, \ldots, K$) are monotonic in r which implies the same for $\Delta_{ijr}^{(k)}$ following Theorem 1. Therefore $\delta = (\boldsymbol{\beta}, \boldsymbol{s}, \boldsymbol{\nu})$ indicates the set of parameters which should be estimated in the proposed JOMRE model.

2.3 Joint likelihood and maximum likelihood estimation

Based on the random-effects framework for joint modeling, the likelihood contribution of the ith subject in the JOMRE model is given by

$$L_i(\delta) = \int_{\boldsymbol{b}} \prod_{j=1}^{n_i} \prod_{k=1}^{K} f\left(Y_{ij}^{(k)} | b_i^{(k)}\right) f(\boldsymbol{b_i}) \mathrm{d}\boldsymbol{b_i}, \quad k = 1, \ldots, K \tag{8}$$

where $f(.)$ is a joint probability distribution of random effects, a multivariate normal in this case, and $f(Y_{ij}^{(k)} | b_i^{(k)})$ for $k = 1, \ldots, K$ is the so-called partially marginalized density. Note that each temporal process has its own time index and the total number of temporal observation for the two ordinal values processes may differ.

Because the JOMRE model consists of two sets of random effects, we need to integrate over both the normal and beta random variables. Thus, the partially marginalized density $f(Y_{ij}^{(k)} | b_i^{(k)})$ is resulted from integrating conditional probabilities over the beta random effects as follows:

$$f\left(Y_{ij}^{(k)} | b_i^{(k)}\right) = \int_{\theta^{(k)}} f\left(Y_{ij}^{(k)} | b_i^{(k)}, \theta^{(k)}\right) p\left(\theta^{(k)}\right) \mathrm{d}\theta^{(k)}, \quad k = 1, \ldots, K \tag{9}$$

where

$$f\left(Y_{ij}^{(k)} | b_i^{(k)}, \theta^{(k)}\right) = \prod_{r=1}^{R} \left(F_{ijr}\left(b_i^{(k)}, \theta^{(k)}\right) - F_{ijr-1}\left(b_i^{(k)}, \theta^{(k)}\right)\right)^{y_{ijr}^{(k)}}, \quad k = 1, \ldots, K \tag{10}$$

so that $y_{ijr}^{(k)} = 1$ if $y_{ij}^{(k)} = r$ and $y_{ijr}^{(k)} = 0$ otherwise. Note that the partially marginalized density $f(Y_{ij}^{(k)} | b_i^{(k)})$ has a closed form:

$$\begin{aligned} f\left(Y_{ij}^{(k)} | b_i^{(k)}\right) &= \int_{\theta^{(k)}} \left[\prod_{r=1}^{R} \left(F_{ijr}\left(b_i^{(k)}, \theta^{(k)}\right) - F_{ijr-1}\left(b_i^{(k)}, \theta^{(k)}\right)\right)^{y_{ijr}^{(k)}}\right] p\left(\theta^{(k)}\right) \mathrm{d}\theta^{(k)} \\ &= E\left(\theta^{(k)}\right)\left(\omega_{ijr}^{(k)}\right)^{y_{ij1}^{(k)}} \times \prod_{r=2}^{R-1}\left(\omega_{ijr}^{(k)} - \omega_{ijr-1}^{(k)}\right)^{y_{ijr}^{(k)}} \times \left(E^{-1}\left(\theta^{(k)}\right) - \omega_{ijR-1}^{(k)}\right)^{y_{ijR}^{(k)}}, \quad k = 1, \ldots, K \end{aligned} \tag{11}$$

where $\omega_{ijr}^{(k)} = \varphi(\Delta_{ijr}^{(k)} + b_i^{(k)})$. Using equations (8) and (11), the likelihood function $L(\delta)$ takes the form:

$$L(\delta) = \prod_{i=1}^{N} \int_{\boldsymbol{b}} \prod_{j=1}^{n_i} \prod_{k=1}^{K} \left[expit(\nu^{(k)}) \left(\omega_{ijr}^{(k)}\right)^{y_{ij1}^{(k)}} \times \prod_{r=2}^{R-1} \left(\omega_{ijr}^{(k)} - \omega_{ijr-1}^{(k)}\right)^{y_{ijr}^{(k)}} \times \left(\frac{1}{expit(\nu^{(k)})} - \omega_{ijR-1}^{(k)}\right)^{y_{ijR}^{(k)}} \right] f(\boldsymbol{b_i})\, \mathrm{d}\boldsymbol{b_i} \tag{12}$$

There is no closed form for likelihood function in equation (12). Therefore, we use the Gaussian–Hermite quadrature method to approximate $L(\delta)$. Maximizing the log-likelihood function, $\log \mathrm{L}(\delta) = \sum_{i=1}^{N} \log(\mathrm{L}_i(\delta))$, with respect to δ yields the parameter estimates. To this end, we used a quasi-Newton-Raphson method to maximize the $\log \mathrm{L}(\delta)$ in the SAS NLMIXED procedure by defining *tech=quanew*. The "general" option in the MODEL statement in this procedure has a feature named user-defined likelihood that enables us to define our likelihood and implement the JOMRE model.

3 Simulations

This section contains two different assessments for our proposed methodology. We considered two longitudinal ordinal responses for computational ease. First, we study the behaviors of the point estimators in terms of their absolute bias (AB) and mean squared error (MSE). Next, we conduct a power analysis to test a covariate effect based on an approximate Wald test using our model.

3.1 Study of bias and mean squared error

In our primary simulation to study the behaviors of the point estimators of three different marginalized random-effects models in terms of their AB and MSE, we consider four different sample sizes ($N = 10$, $N = 30$, $N = 100$, and $N = 250$) each with the same time points with $n_i = 6$ for the two responses. Bivariate overdispersed longitudinal ordinal data were generated from the proposed model in equations (4) and (5) with "time" and "group" variables as the covariates. The model was specified as:

$$\begin{aligned} logit\ P(Y_{ij}^{(k)} \leq r | \boldsymbol{x_{ij}}) &= \alpha_{0r}^{(k)} + \beta_1^{(k)}.time_{ij} + \beta_2^{(k)}.group_i \\ P(Y_{ij}^{(k)} \leq r | \boldsymbol{x_{ij}}, b_i^{(k)}, \theta^{(k)}) &= \theta^{(k)} \varphi(\Delta_{ijr}^{(k)} + b_i^{(k)}) \end{aligned} \tag{13}$$

for $k = 1, 2,$ where$j = 1, 2, \ldots, 6$, $time_{ij} = (j-1)/10$, and $group_i$ is a binary covariate (0 or 1) randomly generated from a Bernoulli distribution with success probability $p = 0.4$ which was arbitrarily chosen. We considered two sets of true parameter values for the two responses given by $\boldsymbol{\beta}^{(1)} = (\alpha_{01}^{(1)}, \alpha_{02}^{(1)}, \alpha_{03}^{(1)}, \beta_1^{(1)}, \beta_2^{(1)}) = (-0.8, 0.5, 1.6, -0.4, -0.1)$ and $\boldsymbol{\beta}^{(2)} = (\alpha_{01}^{(2)}, \alpha_{02}^{(2)}, \alpha_{03}^{(2)}, \beta_1^{(2)}, \beta_2^{(2)}) = (-0.6, 0.8, 1.5, 1, -0.2)$, respectively. The random effects $\boldsymbol{b_i^T} = (b_i^{(1)}, b_i^{(2)})$ were generated from a bivariate normal distribution with mean 0 and $\boldsymbol{s} = (s_1, s_{12}, s_2) = (1.200, 1.040, 1.004)$. These initial values and the coding of the covariates were motivated in a simulation study of a marginalized model by Lee, Daniels, and Joo[10]; since their modeling did not consist of an overdispersion term, we used the arbitrarily chosen values of the true parameter $\boldsymbol{v} = (v^1, v^2) = (2.2, 2.3)$ for the overdispersion parameters.

We utilized a Monte-Carlo sample size of 1000 and fit three marginalized random-effects models under four each of the four sample sizes (algorithm and SAS-code for generating simulated data is given in Appendix 3). The joint marginalized random-effects models with and without overdispersion (JOMRE and JMRE, respectively) were compared with the independence OMRE model. To fit the independence model, we assumed uncorrelated random effects, that is, $s_{12} = 0$. In order to apply the Gaussian–Hermite quadrature method, we used $Q = 50$ quadrature points for all models. Note that this is sufficient according to the guidelines put forward by Lesaffre and Spiessens.[22] The results are given in Table 1, where we report the AB and MSE over all 1000 Monte-Carlo runs.

As can be seen, when the sample size increases, the MSE values reduce for all three models (Figure 1). The AB and MSE for the proposed JOMRE model were smaller than those in the JMRE model, especially for the variance components. We can see considerable bias in the joint model without overdispersion (JMRE); for example, the percentage relative bias for the variance components s_1, s_2, and s_{12} in the JMRE model (vs. JOMRE) in the case of $N = 100$ are 32.2% (vs. 0.7%), 21.9% (vs. 13.2%), and 54.4% (vs. 2%), respectively. Although, at the first glance one could not observe a considerable difference between joint and separate models, the joint model could capture the correlation between responses. In addition, the data analyst can interpret the results using a single joint model instead of fitting two separate models.

We conducted further secondary simulations and generated bivariate longitudinal ordinal data without overdispersion from the JMRE model by considering two different sample sizes ($N = 30$, $N = 250$) and $n_i = 6$ time points. The true parameter values are the same as the primary simulation, except here the data generating model does not include the overdispersion term. The JOMRE and JMRE models were compared based on 500 Monte-Carlo runs. The results are given in Table 2 and as can be seen, the MSE values are reduced when the

Table 1. Simulation results and behavior of parameter estimators obtained from fitting the JOMRE, JMRE, and OMRE models.

	Parameter	Truth	*JMRE* AB	*JMRE* MSE	*JOMRE* AB	*JOMRE* MSE	*OMRE* AB	*OMRE* MSE
N = 10								
$Y^{(1)}$	Int1	−0.8	**0.114**	0.790	**0.108**	0.331	**0.126**	0.611
	Int2	0.5	**0.070**	0.448	**0.015**	0.200	**0.020**	0.190
	Int3	1.6	**0.138**	0.617	**0.043**	0.212	**0.035**	0.195
	Time	−0.4	**0.060**	1.306	**0.023**	0.548	**0.016**	0.511
	Group	−0.1	**0.009**	0.931	**0.018**	0.400	**0.030**	0.386
	Overdispersion	2.2	***NA***	*NA*	**1.163**	17.792	**1.058**	15.784
$Y^{(2)}$	Int1	−0.6	**0.033**	0.808	**0.049**	0.243	**0.046**	0.265
	Int2	0.8	**0.036**	1.125	**0.066**	0.209	**0.062**	0.220
	Int3	1.5	**0.000**	1.377	**0.054**	0.220	**0.056**	0.216
	Time	1	**0.079**	1.556	**0.021**	0.547	**0.024**	0.521
	Group	−0.2	**0.069**	1.717	**0.066**	0.428	**0.054**	0.433
	Overdispersion	2.3	***NA***	*NA*	**1.384**	19.718	**1.291**	18.082
Variance Components	s_1	1.2	**0.444**	0.320	**0.002**	0.288	**0.011**	0.942
	s_2	1.004	**0.271**	0.192	**0.151**	0.134	**0.112**	0.252
	s_{12}	1.04	**0.560**	0.506	**0.154**	1.356	***NA***	*NA*
N = 30								
$Y^{(1)}$	Int1	−0.8	**0.013**	0.145	**0.020**	0.107	**0.025**	0.108
	Int2	0.5	**0.056**	0.122	**0.012**	0.085	**0.006**	0.084
	Int3	1.6	**0.040**	0.132	**0.028**	0.095	**0.020**	0.093
	Time	−0.4	**0.026**	0.411	**0.012**	0.251	**0.015**	0.252
	Group	−0.1	**0.007**	0.257	**0.017**	0.158	**0.010**	0.160
	Overdispersion	2.2	***NA***	*NA*	**0.162**	1.323	**0.196**	2.002
$Y^{(2)}$	Int1	−0.6	**0.005**	0.138	**0.000**	0.097	**0.001**	0.099
	Int2	0.8	**0.032**	0.130	**0.063**	0.093	**0.061**	0.093
	Int3	1.5	**0.065**	0.137	**0.071**	0.100	**0.069**	0.098
	Time	1	**0.013**	0.486	**0.042**	0.286	**0.037**	0.279
	Group	−0.2	**0.039**	0.251	**0.038**	0.155	**0.036**	0.164
	Overdispersion	2.3	***NA***	*NA*	**0.182**	1.099	**0.174**	1.024
Variance Components	s_1	1.2	**0.399**	0.188	**0.017**	0.052	**0.014**	0.053
	s_2	1.004	**0.236**	0.088	**0.125**	0.071	**0.123**	0.075
	s_{12}	1.04	**0.567**	0.360	**0.006**	0.155	***NA***	*NA*
N = 100								
$Y^{(1)}$	Int1	−0.8	**0.006**	0.037	**0.010**	0.031	**0.013**	0.031
	Int2	0.5	**0.043**	0.035	**0.005**	0.027	**0.002**	0.028
	Int3	1.6	**0.013**	0.037	**0.011**	0.030	**0.007**	0.032
	Time	−0.4	**0.022**	0.118	**0.009**	0.085	**0.008**	0.084
	Group	−0.1	**0.000**	0.075	**0.000**	0.056	**0.000**	0.058
	Overdispersion	2.2	***NA***	*NA*	**0.011**	0.048	**0.011**	0.050
$Y^{(2)}$	Int1	−0.6	**0.025**	0.039	**0.023**	0.032	**0.021**	0.033
	Int2	0.8	**0.042**	0.038	**0.063**	0.035	**0.064**	0.036
	Int3	1.5	**0.087**	0.045	**0.082**	0.039	**0.082**	0.039
	Time	1	**0.025**	0.136	**0.046**	0.095	**0.044**	0.095
	Group	−0.2	**0.022**	0.067	**0.015**	0.049	**0.016**	0.052
	Overdispersion	2.3	***NA***	*NA*	**0.022**	0.054	**0.021**	0.055
Variance components	s_1	1.2	**0.387**	0.158	**0.009**	0.015	**0.008**	0.015
	s_2	1.004	**0.220**	0.057	**0.133**	0.035	**0.131**	0.034
	s_{12}	1.04	**0.566**	0.332	**0.021**	0.048	***NA***	*NA*
N = 250								
$Y^{(1)}$	Int1	−0.8	**0.010**	0.016	**0.007**	0.013	**0.004**	0.013
	Int2	0.5	**0.049**	0.016	**0.012**	0.012	**0.009**	0.012

(continued)

Table 1. Continued

	Parameter	Truth	*JMRE* AB	*JMRE* MSE	*JOMRE* AB	*JOMRE* MSE	*OMRE* AB	*OMRE* MSE
	Int3	1.6	**0.012**	0.015	**0.012**	0.013	**0.009**	0.013
	Time	−0.4	**0.017**	0.047	**0.004**	0.033	**0.003**	0.033
	Group	−0.1	**0.009**	0.027	**0.013**	0.020	**0.010**	0.021
	Overdispersion	2.2	***NA***	*NA*	**0.011**	0.018	**0.011**	0.019
$Y^{(2)}$	Int1	−0.6	**0.035**	0.016	**0.031**	0.014	**0.031**	0.014
	Int2	0.8	**0.036**	0.016	**0.059**	0.016	**0.060**	0.016
	Int3	1.5	**0.088**	0.022	**0.084**	0.020	**0.084**	0.020
	Time	1	**0.036**	0.052	**0.051**	0.040	**0.050**	0.040
	Group	−0.2	**0.016**	0.027	**0.009**	0.019	**0.010**	0.020
	Overdispersion	2.3	***NA***	*NA*	**0.009**	0.018	**0.008**	0.019
Variance components	s_1	1.2	**0.378**	0.146	**0.002**	0.006	**0.002**	0.006
	s_2	1.004	**0.211**	0.049	**0.143**	0.027	**0.143**	0.027
	s_{12}	1.04	**0.558**	0.316	**0.009**	0.020	***NA***	*NA*

JMRE: joint marginalized random effects; JOMRE: joint overdispersed marginalized random effects; OMRE: overdispersed marginalized random effects. Bivariate longitudinal and overdispersed ordinal data were generated from the JOMRE model. Here, AB is absolute value of bias and MSE is mean squared error based on 1000 Monte-Carlo runs.

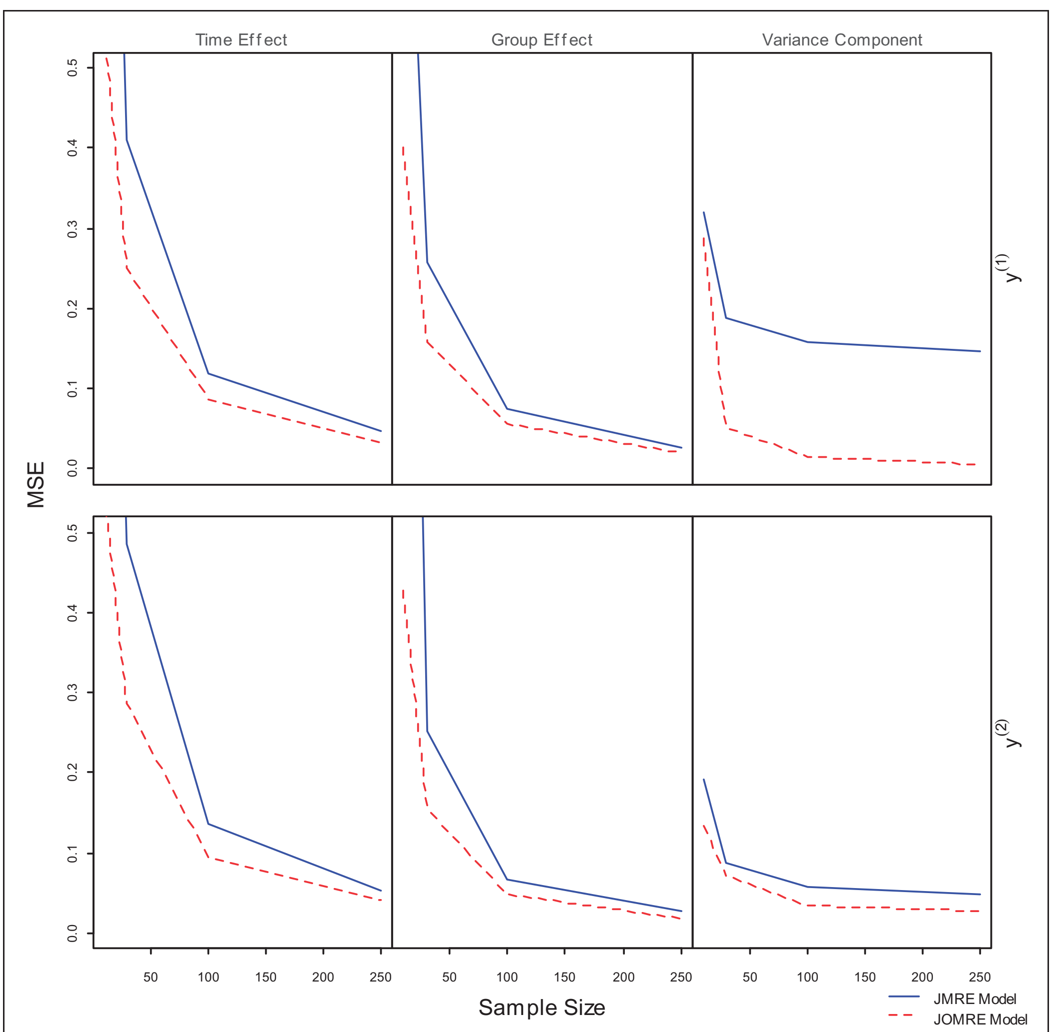

Figure 1. Plot of MSE against sample size based on the 1000 Monte-Carlo replicates. The solid-blue line corresponds to the JMRE model and the dashed-red line corresponds to the proposed JOMRE model.

Table 2. Simulation results obtained from fitting the JOMRE and JMRE models.

	Parameter	Truth	*JMRE* AB	*JMRE* MSE	*JOMRE* AB	*JOMRE* MSE
N = 30						
$Y^{(1)}$	Int1	−0.8	0.0341	0.0835	0.034	0.083
	Int2	0.5	0.0028	0.0703	0.002	0.070
	Int3	1.6	0.0479	0.0929	0.052	0.093
	Time	−0.4	0.0329	0.1641	0.034	0.163
	Group	−0.1	0.0209	0.1606	0.018	0.161
$Y^{(2)}$	Int1	−0.6	0.0107	0.0662	0.011	0.065
	Int2	0.8	0.0758	0.0761	0.076	0.075
	Int3	1.5	0.0946	0.0920	0.092	0.090
	Time	1	0.0104	0.1789	0.018	0.177
	Group	−0.2	0.0673	0.1522	0.067	0.155
Variance components	s_1	1.2	0.0220	0.0238	0.002	0.024
	s_2	1.004	0.1213	0.0382	0.140	0.044
	s_{12}	1.04	0.0223	0.0789	0.011	0.082
N = 250						
$Y^{(1)}$	Int1	−0.8	0.0002	0.0140	0.0000	0.0070
	Int2	0.5	0.0059	0.0128	0.0053	0.0064
	Int3	1.6	0.0146	0.0170	0.0150	0.0086
	Time	−0.4	0.0105	0.0323	0.0106	0.0162
	Group	−0.1	0.0016	0.0306	0.0016	0.0153
$Y^{(2)}$	Int1	−0.6	0.0435	0.0154	0.0437	0.0086
	Int2	0.8	0.0527	0.0174	0.0529	0.0101
	Int3	1.5	0.1055	0.0291	0.1050	0.0200
	Time	1	0.0793	0.0428	0.0805	0.0248
	Group	−0.2	0.0241	0.0311	0.0240	0.0157
Variance components	s_1	1.2	0.0042	0.0054	0.0014	0.0027
	s_2	1.004	0.1450	0.0265	0.1515	0.0258
	s_{12}	1.04	0.0112	0.0176	0.0006	0.0088

JMRE: joint marginalized random effects; JOMRE: joint overdispersed marginalized random effects. Bivariate longitudinal ordinal data without overdispersion were generated from the JMRE model. Here AB is absolute value of bias and MSE is mean squared error based on 500 Monte-Carlo runs.

sample size increases. The AB and MSE for the proposed JOMRE model were still smaller than those in the JMRE model.

We also conducted another secondary simulation and generated bivariate longitudinal ordinal data from the JOMRE model, in which overdispersion parameter is added to only one of the two responses, $Y^{(1)}$, by considering two different sample sizes ($N = 30$, $N = 250$) and $n_i = 6$ time points. The true parameter values are the same as the main simulation, except here the generating model does not include the overdispersion parameter for the second response, $Y^{(2)}$. The JOMRE and JMRE models are compared based on 500 Monte-Carlo runs. The results are given in Table 3 and as can be seen, the proposed JOMRE model is still superior to the JMRE model in terms of MSE and AB.

Overall, the simulation shows the considerable biases that can occur in the marginal and subject-specific parameters when the overdispersion is not captured in longitudinal ordinal data.

3.2 Power analysis for testing a covariate effect

We assess the statistical power of the Wald test for $H_0 : \beta_1^{(k)} = 0$ (for $k = 1, 2$) using the JOMRE model with 1000 Monte-Carlo replicates. Further simulations were conducted using additional values of the $\beta_1^{(k)}$ parameters and bivariate overdispersed longitudinal ordinal data were generated from the same model as in equation (13). Figure 2

Table 3. Simulation results obtained from fitting the JOMRE and JMRE models.

	Parameter	Truth	JMRE		JOMRE	
			AB	MSE	AB	MSE
N = 30						
$Y^{(1)}$	Int1	−0.8	0.018	0.075	0.020	0.063
	Int2	0.5	0.056	0.063	0.021	0.051
	Int3	1.6	0.047	0.069	0.046	0.060
	Time	−0.4	0.045	0.209	0.029	0.145
	Group	−0.1	0.014	0.131	0.008	0.096
	Overdispersion	2.2	*NA*	*NA*	0.260	1.108
$Y^{(2)}$	Int1	−0.6	0.008	0.068	0.011	0.059
	Int2	0.8	0.073	0.077	0.084	0.070
	Int3	1.5	0.092	0.093	0.105	0.086
	Time	1	0.011	0.179	0.034	0.166
	Group	−0.2	0.065	0.160	0.057	0.138
Variance components	s1	1.2	0.393	0.169	0.019	0.027
	s2	1.004	0.122	0.038	0.152	0.046
	s12	1.04	0.342	0.155	0.009	0.084
N = 250						
$Y^{(1)}$	Int1	−0.8	0.007	0.007	0.003	0.006
	Int2	0.5	0.048	0.009	0.009	0.006
	Int3	1.6	0.014	0.007	0.013	0.006
	Time	−0.4	0.018	0.023	0.009	0.016
	Group	−0.1	0.005	0.014	0.008	0.010
	Overdispersion	2.2	*NA*	*NA*	0.011	0.009
$Y^{(2)}$	Int1	−0.6	0.043	0.009	0.044	0.009
	Int2	0.8	0.054	0.011	0.053	0.010
	Int3	1.5	0.107	0.021	0.105	0.020
	Time	1	0.080	0.025	0.081	0.025
	Group	−0.2	0.024	0.017	0.021	0.015
Variance components	s1	1.2	0.380	0.146	0.004	0.003
	s2	1.004	0.145	0.024	0.152	0.026
	s12	1.04	0.336	0.117	0.004	0.009

JMRE: joint marginalized random effects; JOMRE: joint overdispersed marginalized random effects. Bivariate longitudinal ordinal data were generated from the proposed model and overdispersion parameter is added to only one of two responses ($Y^{(1)}$). Here, AB is absolute value of bias and MSE is mean squared error based on 500 Monte-Carlo runs.

shows the power curves corresponding to the JOMRE model for two sample sizes, namely, $N = 30$ and $N = 250$. Clearly, the power increases as the alternative values are further away from the null. We can also see that the power improves as the sample size increases.

When the true values of $\beta_1^{(k)}$ are 0, the empirical size (95% CI for size) of the tests for $\beta_1^{(1)}$ and $\beta_1^{(2)}$ are 0.044 (0.032, 0.056) and 0.050 (0.037, 0.063), respectively, which are extremely close to the target nominal size $\alpha = 0.05$.

4 Analysis of SSc data

4.1 Data

We use data from 156 systemic sclerosis patients from Firoozgar General Hospital in Tehran to make inference about SSc severity based on the Medsger severity scale.[20] For each patient, we selected two of the most important Medsger scale items, namely, GS and SS, as two correlated responses measured three times from 2013 to 2015. Severity scale items were categorized from 0 (no documented involvement) to 4 (endstage disease) for each organ system. GS was categorized based on the hemoglobin (Hb) as follows: "0" (normal) when Hb is 12.3 Gm/dl or greater, "1" (mild) when Hb is 11.0–12.3 Gm/dl, "2" (moderate) when Hb is 9.7–11.0 Gm/dl, "3" (severe) when Hb is 8.3–9.7 Gm/dl, and "4" (endstage) when Hb is less than 8.3 Gm/dl. SS variable was also categorized based

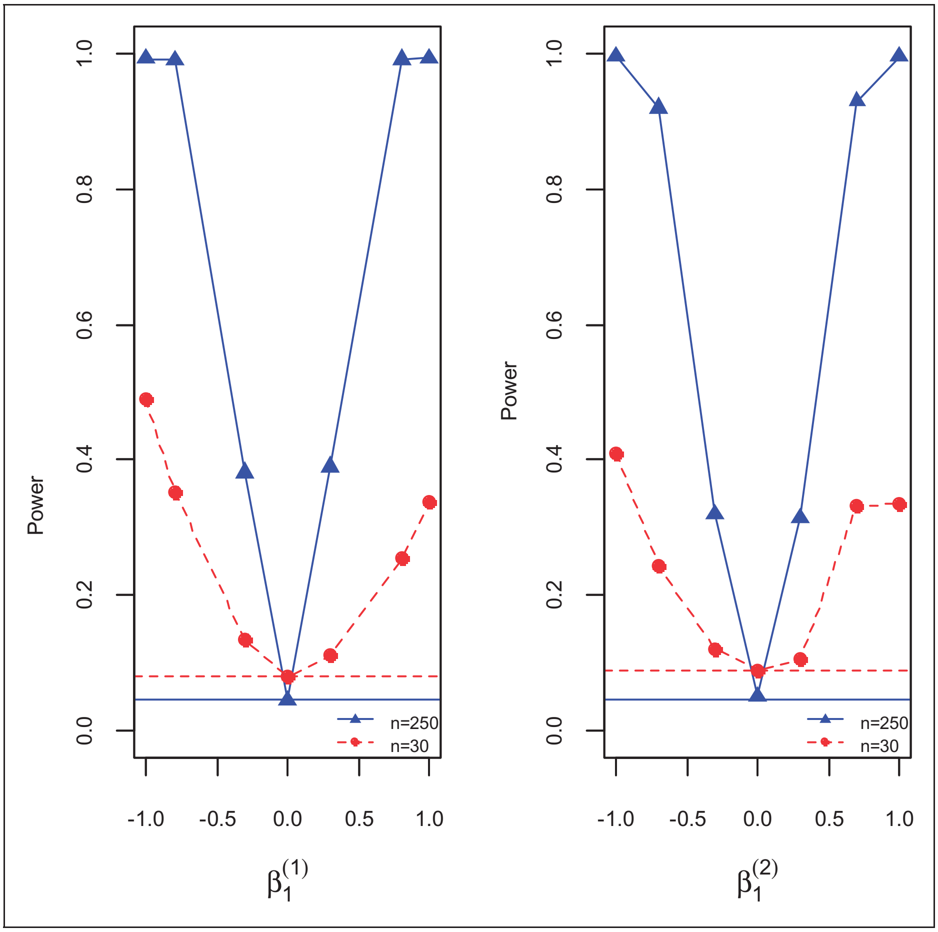

Figure 2. The power plots for testing the effect of covariate time using the JOMRE model based on the Monte-Carlo sample size of 1000. The solid-blue line corresponds to $N = 250$ and the dashed-red line corresponds to $N = 30$. Also, the left curve corresponds to the first response and the right curve corresponds to the second response. The horizontal lines denote the nominal sizes.

on the modified Rodnan Total Skin thickness Score (TSS) as follows: "0" when TSS is 0, "1" when TSS is 1–14, "2" when TSS is 15–29, "3" when TSS is 30–39, and "4" when TSS is greater than or equal to 40. Table 4 presents the frequency distribution of GS and SS over time.

4.2 Model fit

Let $Y_{ij}^{(1)}$ and $Y_{ij}^{(2)}$ indicate the GS and SS variables, respectively, with $r = 0, \ldots, 4$ ordered categories for the ith subject at the jth time of measurements ($i = 1, 2, \ldots, 156; j = 1, 2, 3$). We coded gender as a covariate taking values "0" for female and "1" for male. We fitted three models, namely, JMRE, JOMRE, and OMRE. The JMRE and JOMRE models include correlated normal intercepts to account the correlation between two organs (GS and SS) for the same patient and additionally, the JOMRE model includes independent beta random variables to model potential overdispersion in our longitudinal ordinal data. Applying our model (equation (4)), the marginal parts of these models can be written as:

$$logitP(GS_{ij} \leq r|\boldsymbol{x_{ij}}) = \alpha_{0r}^{(1)} + \beta_1^{(1)} time_{ij} + \beta_2^{(1)} gender_i$$
$$logitP(SS_{ij} \leq r|\boldsymbol{x_{ij}}) = \alpha_{0r}^{(2)} + \beta_1^{(2)} time_{ij} + \beta_2^{(2)} gender_i$$

where $\alpha_{0r}^{(k)}$, $k = 1, 2$, are intercepts and $(\beta_1^{(k)}, \beta_2^{(k)})$ are fixed effects with population-averaged interpretation. We used the SAS NLMIXED procedure for fitting these models. The initial values of the parameters were obtained from fitting the univariate fixed-effects models. SAS code for all models in both univariate and

Table 4. Frequency distribution of general system (GS) and skin system (SS) of SSc patients ($N = 156$).

	Time					
	2013		2014		2015	
Category	GS	SS	GS	SS	GS	SS
0 (Normal)	95 (61.3)	18 (11.7)	92 (59.7)	25 (16.1)	89 (57.1)	31 (20.0)
1 (Mild)	56 (36.1)	108 (70.1)	53 (34.4)	112 (72.3)	56 (35.9)	98 (63.3)
2 (Moderate)	2 (1.4)	26 (16.8)	7 (4.5)	17 (11.0)	9 (5.8)	25 (16.1)
3 (Severe)	1 (0.6)	2 (1.4)	2 (1.4)	1 (0.6)	1 (0.6)	1 (0.6)
4 (Endstage)	1 (0.6)	0	0	0	1 (0.6)	0
Total	155	154	154	155	156	155

[a]n (%)

Table 5. Maximum likelihood estimates for SSc data.

		JMRE		*JOMRE*		*OMRE*	
	Parameter	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value
General system (SS)							
	Intercept 0 $\left(\alpha_{01}^{(1)}\right)$	−2.0 (0.26)	<0.001	−1.9 (0.24)	<0.001	−1.9 (0.24)	<0.001
	Intercept 1 $\left(\alpha_{02}^{(1)}\right)$	1.3 (0.23)	<0.001	1.4 (0.22)	<0.001	1.4 (0.23)	<0.001
	Intercept 2 $\left(\alpha_{03}^{(1)}\right)$	4.0 (0.53)	<0.001	4.3 (0.50)	<0.001	4.3 (0.50)	<0.001
	Time $\left(\beta_{1}^{(1)}\right)$	0.2 (0.08)	0.014	0.1 (0.07)	0.033	0.1 (0.07)	0.033
	Gender $\left(\beta_{2}^{(1)}\right)$	0.1 (0.44)	0.849	0.2 (0.45)	0.729	0.1 (0.46)	0.786
	Overdispersion $(\nu^{(1)})$	*NA*	*NA*	5.3 (0.71)	<0.001	5.3 (0.71)	<0.001
Skin system (GS)							
	Intercept 0 $\left(\alpha_{01}^{(2)}\right)$	0.5 (0.20)	0.015	0.5 (0.20)	0.016	0.5 (0.20)	0.016
	Intercept 1 $\left(\alpha_{02}^{(2)}\right)$	3.0 (0.32)	<0.001	3.0 (0.32)	<0.001	3.0 (0.32)	<0.001
	Intercept 2 $\left(\alpha_{03}^{(2)}\right)$	4.6 (0.55)	<0.001	4.6 (0.55)	<0.001	4.6 (0.52)	<0.001
	Intercept 3 $\left(\alpha_{04}^{(2)}\right)$	5.8 (0.82)	<0.001	5.8 (0.82)	<0.001	5.7 (0.77)	<0.001
	Time $\left(\beta_{1}^{(2)}\right)$	−0.1 (0.07)	0.102	−0.1 (0.07)	0.103	−0.1 (0.07)	0.104
	Gender $\left(\beta_{2}^{(2)}\right)$	1.5 (0.53)	0.005	1.5 (0.52)	0.005	1.5 (0.54)	0.005
	Overdispersion $(\nu^{(2)})$	*NA*	*NA*	19.5 (941.57)	0.983	18.0 (439.28)	0.967
Variance components							
	s_1	1.8 (0.20)	<0.001	2.4 (0.38)	<0.001	2.4 (0.38)	<0.001
	s_2	1.8 (0.21)	<0.001	1.8 (0.21)	<0.001	1.8 (0.23)	<0.001
	Rho	0.2 (0.10)	0.054	0.2 (0.10)	0.067	*NA*	*NA*
Fit statistics							
	AIC	1322.4		1303.8		1305.2	
	Loglik	−647.2		−635.9		−637.6	

SSc: systemic sclerosis; JMRE: joint marginalized random effects; JOMRE: joint overdispersed marginalized random effects; OMRE: overdispersed marginalized random effects.

bivariate cases are given in Appendix 4. Table 5 provides the maximum likelihood estimates and goodness of fit statistics for these three models.

From the perspective of model selection, both Loglik and AIC indicate that the JOMRE model offers the best fit for these data, although the JOMRE and OMRE models resulted in similar estimates. Presumably, it means that the joint marginalized random-effects model was improved by considering the overdispersion parameter. The difference in deviance for the JMRE versus the JOMRE model is 22.6 (P-value$<$0.001 on one degree of freedom) which shows that the joint model with overdispersion has a statistically significantly better fit than the simple model without overdispersion. On the other hand, the difference in deviance for the JOMRE versus the OMRE model is 3.4 (P-value$=$0.065 on one degree of freedom) which is borderline non-significant.

The point estimate of the overdispersion parameter in the JOMRE model was significant for SS response ($\nu^{(1)} = 5.3$, $SE = 0.71$, P-value $<$0.001). There were some differences in the marginal and random-effects parameter estimates between the JOMRE and JMRE models for SS response variable due to the significant overdispersion in this outcome. On the other hand, the overdispersion parameter was not significant for GS response ($\nu^{(2)} = 19.5$, $SE = 941.57$, P-value$=$0.983) and, as a result, both the JMRE and JOMRE models produced almost the same parameter estimates for this outcome. The variance components, s_1 and s_2, were both significant which confirms the use of random-effects parts in the marginalized models. The effect of gender on GS was significant ($\beta_2^{(2)} = 1.5$, $SE = 0.52$, P-value$=$0.005) which indicates that the log-odds of GS below any given level was higher for males than for females. Finally, the effect of time on SS was significant ($\beta_2^{(2)} = 0.1$, $SE = 0.07$, P-value$=$0.033) which shows that the log-odds of SS below any given level increases as time increases.

5 Conclusion

We have considered analyzing two or more correlated longitudinal ordinal outcome processes and proposed a joint overdispersed marginalized random-effects model for the same. This model combines the advantages of marginalized random-effects framework to directly model the marginal probabilities as a function of covariates. In addition, this model uses normal random effects to handle the correlation between responses, as well as beta random effects to deal with overdispersion in longitudinal-ordered categorical data.

Using simulations, we demonstrated superior performance of the JOMRE model compared with the JMRE model and also showed that both the bias and the overall mean squared error of our estimators diminish as the number of subject increases. Our position is that having it does not hurt and generally produces better results, albeit slightly in some cases. At the end, we leave it up to the modeler to decide whether to include the overdispersion term or not by looking at the model result.

On the data analysis front, we showed that the proposed JOMRE model had a better fit than the simpler JMRE model. We also found that higher levels of skin system and SSc severity is higher in females than males.

In principle, this methodology can directly be fitted for more than two responses; however, a limitation of likelihood-based approach is the difficulty of incorporating several random effects since the dimension of the integrals is high and computationally expensive. Extending this methodology to a Bayesian framework may be a way around in such situations. We also can extend this model to allow the correlated beta random effects through the multivariate beta distribution. We will explore these possibilities elsewhere.

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Appendix 1

The proof of Theorem 1 in Section 2.1

Theorem 1. In the OMRE model given by equation (1), if $\alpha_{01} < \cdots < \alpha_{0R-1}$, then $\Delta_{ij1} < \cdots < \Delta_{ijR-1}$.

Proof. Based on the closed form of Δ_{ijr} in equation (3) we can write that

$$\Delta_{ijr} = \Phi^{-1}\left\{{}^{1}\!/_{E(\theta)}\, expit(\alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta})\right\} \times \left\{\sqrt{1+s^2}\right\} \sim \Phi^{-1}(expit(\alpha_{0r})) \tag{14}$$

where $expit(\alpha_{0r}) = \dfrac{\exp(\alpha_{0r})}{1+\exp(\alpha_{0r})}$ is an increasing function between 0 and 1 for all α_{0r}, thus if $\alpha_{01} < \cdots < \alpha_{0R-1}$ then

$$expit(\alpha_{01}) < \cdots < expit(\alpha_{0R-1}) \tag{15}$$

Also, $\Phi^{-1}(.)$ is an increasing function and thus

$$\Phi^{-1}(expit(\alpha_{01})) < \cdots < \Phi^{-1}(expit(\alpha_{0R-1})) \tag{16}$$

Thus, relation (16) results in $\Delta_{ij1} < \cdots < \Delta_{ijR-1}$.

Appendix 2

This Appendix consists of computational details of the connector in the OMRE and JOMRE models. We substantially added some arguments to extend the definition and closed form of the connector from the binary response[21] to the ordinal response.

Appendix 2.1

Computational details of the connector Δ_{ijr}: Combining marginal and overdispersed random-effects models into a single OMRE model.

The connector, Δ_{ijr}, connects the marginal and overdispersed random-effects models and can be calculated from the relationship between the marginal and conditional probabilities as follows:

$$F_{ijr} = \int_b \int_\theta F_{ijr}(b_i, \theta)\, p(\theta)\, f(b_i)\, \mathrm{d}\theta\, \mathrm{d}b_i$$

then based on equation (1) we can write:

$$\begin{aligned} \alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta} &= Logit\left[\int_b \int_\theta \theta\Phi\big(\Delta_{ijr} + b_i\big)\, p(\theta)\, f(b_i)\, \mathrm{d}\theta\, \mathrm{d}b_i\right] \\ \alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta} &= Logit\left[\int_b E(\theta)\Phi\big(\Delta_{ijr} + b_i\big)\, f(b_i)\, \mathrm{d}b_i\right], \\ \alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta} &= Logit\left[E(\theta)\int_b \Phi\big(\Delta_{ijr} + b_i\big)\, f(b_i)\, \mathrm{d}b_i\right] \end{aligned} \tag{17}$$

where $\int \Phi\big(\Delta_{ijr} + b_i\big)\, f(b_i)\, \mathrm{d}b_i = \Phi(\frac{\Delta_{ijr}}{\sqrt{1+s^2}})$ (calculation detail is given in sub-section 2.2)

$$\begin{aligned} \alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta} &= Logit\left[E(\theta)\Phi(\frac{\Delta_{ijr}}{\sqrt{1+s^2}})\right], \\ expit\left[\alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta}\right] &= E(\theta)\Phi\left(\frac{\Delta_{ijr}}{\sqrt{1+s^2}}\right), \\ \frac{1}{E(\theta)} expit\left[\alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta}\right] &= \Phi\left(\frac{\Delta_{ijr}}{\sqrt{1+s^2}}\right), \\ \Phi^{-1}\left[\frac{1}{E(\theta)} expit\left\{\alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta}\right\}\right] &= \frac{\Delta_{ijr}}{\sqrt{1+s^2}}, \\ \Delta_{ijr} &= \Phi^{-1}\left[\frac{1}{E(\theta)} expit\left\{\alpha_{0r} + \boldsymbol{x}_{ij}^{T}\boldsymbol{\beta}\right\}\right] \times \sqrt{1+s^2} \end{aligned}$$

Appendix 2.2

Proof of $\int \Phi\big(\Delta_{ijr} + b_i\big)\, f(b_i)\, \mathrm{d}b_i = \Phi(\frac{\Delta_{ijr}}{\sqrt{1+s^2}})$ in equation (17)

We know that

$$\Phi(x) = \int_{-\infty}^{x} \frac{1}{\sqrt{2\pi}} \exp(\frac{-t^2}{2})\mathrm{d}t$$

then

$$\begin{aligned} \int \Phi\big(\Delta_{ijr} + b_i\big)\, f(b_i)\, \mathrm{d}b_i &= \int_{-\infty}^{+\infty}\int_{-\infty}^{\Delta_{ijr}+b_i} \frac{1}{\sqrt{2\pi}} exp\left(\frac{-t^2}{2}\right). \frac{1}{\sqrt{2\pi}s} exp\left(\frac{-b_i^2}{2s^2}\right)\mathrm{d}t\mathrm{d}b_i, \\ &= \int_{-\infty}^{+\infty}\int_{-\infty}^{\Delta_{ijr}+b_i} \left(\frac{1}{\sqrt{2\pi}}\right)^2 \frac{1}{s} exp\left\{\frac{-1}{2}\left[b_i^2 s^{-2} + \left(t^2\right)\right]\right\}\mathrm{d}t\mathrm{d}b_i \end{aligned}$$

Here, we make a change of variable $z = t - b_i$ and then

$$= \int_{-\infty}^{+\infty}\int_{-\infty}^{\Delta_{rij}} \left(\frac{1}{\sqrt{2\pi}}\right)^2 \frac{1}{s} exp\left\{\frac{-1}{2}\left[b_i^2 s^{-2} + (z + b_i)^2\right]\right\}\mathrm{d}z\mathrm{d}b_i$$

Further, let us define:

$$\begin{cases} A = 1 + s^{-2} \\ B = -\frac{z}{s^{-2}} \\ C = z^2 E \\ E = \frac{1}{1+s^2} \end{cases}$$

then

$$= \int_{-\infty}^{+\infty} \int_{-\infty}^{\Delta_{rij}} \left(\frac{1}{\sqrt{2\pi}}\right)^2 \frac{1}{s} exp\left\{\frac{-1}{2}\left[b_i^2 A + 2zb_i + z^2\right]\right\} \mathrm{d}z\mathrm{d}b_i$$

Consider that $b_i^2 s^{-2} + (z + b_i)^2 = b_i^2 A + 2zb_i + z^2 = (b_i - B)^2 A + C$, and then

$$= \int_{-\infty}^{+\infty} \int_{-\infty}^{\Delta_{rij}} \left(\frac{1}{\sqrt{2\pi}}\right)^2 \frac{1}{s} exp\left\{\frac{-1}{2} \frac{(b_i - B)^2}{\frac{1}{A}}\right\}.exp\left\{\frac{-1}{2} \frac{z^2}{\frac{1}{E}}\right\} \mathrm{d}z\mathrm{d}b_i$$

by multiplying the above formula with $\frac{1}{A^{\frac{1}{2}} A^{\frac{-1}{2}} E^{\frac{1}{2}} E^{-\frac{1}{2}}}$, we then have

$$= \int_{-\infty}^{+\infty} \int_{-\infty}^{\Delta_{rij}} \frac{1}{A^{\frac{1}{2}} A^{\frac{-1}{2}} E^{\frac{1}{2}} E^{-\frac{1}{2}}} \cdot \left(\frac{1}{\sqrt{2\pi}}\right)^2 \frac{1}{s} exp\left\{\frac{-1}{2} \frac{(b_i - B)^2}{\frac{1}{A}}\right\}.exp\left\{\frac{-1}{2} \frac{z^2}{\frac{1}{E}}\right\} \mathrm{d}z\mathrm{d}b_i$$

$$= \frac{1}{A^{\frac{1}{2}} E^{\frac{1}{2}} s} \int_{-\infty}^{+\infty} \int_{-\infty}^{\Delta_{rij}} \frac{1}{\sqrt{2\pi} A^{\frac{-1}{2}}} exp\left\{\frac{-1}{2} \frac{(b_i - B)^2}{\frac{1}{A}}\right\}. \frac{1}{\sqrt{2\pi} E^{\frac{-1}{2}}} exp\left\{\frac{-1}{2} \frac{z^2}{\frac{1}{E}}\right\} \mathrm{d}z\mathrm{d}b_i$$

$$= 1 \times \int_{-\infty}^{+\infty} \frac{1}{\sqrt{2\pi} A^{\frac{-1}{2}}} exp\left\{\frac{-1}{2} \frac{(b_i - B)^2}{\frac{1}{A}}\right\} \mathrm{d}b_i \int_{-\infty}^{\Delta_{rij}} \frac{1}{\sqrt{2\pi} E^{\frac{-1}{2}}} exp\left\{\frac{-1}{2} \frac{z}{\frac{1}{E}}\right\} \mathrm{d}z$$

$$= 1 \times 1 \times \int_{-\infty}^{\Delta_{rij}} \frac{1}{\sqrt{2\pi} E^{\frac{-1}{2}}} exp\left\{\frac{-1}{2} \frac{z^2}{\frac{1}{E}}\right\} \mathrm{d}z$$

Here, we make a change of variable $= z\frac{1}{\sqrt{E}}$, and then

$$= 1 \times 1 \times \int_{-\infty}^{\frac{\Delta_{rij}}{\sqrt{1+s^2}}} \frac{1}{\sqrt{2\pi} E^{\frac{-1}{2}}} exp\left\{\frac{-1}{2} q^2\right\} E^{\frac{-1}{2}} \mathrm{d}q,$$

$$= 1 \times 1 \times \int_{-\infty}^{\frac{\Delta_{rij}}{\sqrt{1+s^2}}} \frac{1}{\sqrt{2\pi}} exp\left\{\frac{-q^2}{2}\right\} \mathrm{d}q,$$

$$= \Phi\left(\frac{\Delta_{rij}}{\sqrt{1+s^2}}\right)$$

Appendix 3

SAS code for generating simulated data based on the proposed JOMRE model.

```
data sim;
call streaminit(1234);

do ss=1 to 1000 ; *Monte-Carlo Sample Size;

mean1=0; *Mean for random-effect u1;
mean2=0; *Mean for random-effect u2;
```

```
sig1=1.20; *SD for u1;
sig2=1.004; *SD for u2;
rho=0.86; *Correlation between u1 & u2;
a01=-0.8; *Initial value for intercept_cat_1_for y1;
a02=0.5; *Initial value for intercept_cat_2_for y1;
a03=1.6; *Initial value for intercept_cat_3_for y1;
a1=-0.4; *Initial value for time for y1;
a2=-0.1; *Initial value for group for y1;
q1=2.2; *Initial value for Overdispersion par. for y1;
nu1=exp(q1)/(1+exp(q1));
c01=-0.6; *Initial value for intercept_cat_1_for y2;
c02=0.8; *Initial value for intercept_cat_2_for y2;
c03=1.5; *Initial value for intercept_cat_3_for y2;
c1=1; *Initial value for time for y2;
c2=-0.2; *Initial value for group for y2;
q2=2.3; *Initial value for Overdispersion par. for y2;
nu2 = exp(q2)/(1+exp(q2));

do kk=1 to 250; *IndividualNumber_N;

group = rand(''Bernoulli'',0.4); *Generating a group variable;
r1 = rand(''Normal'',0,1);
r2 = rand(''Normal'',0,1.5);
u1 = mean1 + r1*sig1;
u2 = (mean2 + sig2*rho*r1) + (sqrt(sig2*sig2-sig2*sig2*rho*rho)*r2);

do TT=1 to 6; *TimePoints_J;

sim=ss;
id=kk;
time=(TT-1)/10;

*__Mimic-Model for Y1__*;
eta1_1 = a01 + a1*time + a2*group;
pm1_1=exp(eta1_1)/(1+exp(eta1_1));
eta1_2 = a02 + a1*time + a2*group;
pm1_2=exp(eta1_2)/(1+exp(eta1_2));
eta1_3 = a03 + a1*time + a2*group;
pm1_3=exp(eta1_3)/(1+exp(eta1_3));
delta1_1 = sqrt(1+(sig1*sig1)) * probit((1/nu1)*pm1_1);
delta1_2 = sqrt(1+(sig1*sig1)) * probit((1/nu1)*pm1_2);
delta1_3 = sqrt(1+(sig1*sig1)) * probit((1/nu1)*pm1_3);
  p1=nu1 * probnorm(delta1_1 + u1);
  p2=(nu1 * probnorm(delta1_2 + u1))- (nu1 * probnorm(delta1_1 + u1));
  p3=(nu1 * probnorm(delta1_3 + u1))- (nu1 * probnorm(delta1_2 + u1));
  p4=1- (nu1 * probnorm(delta1_3 + u1));

*__Mimic-Model for Y2__*;
eta2_1 = c01 + c1*time + c2*group;
pm2_1=exp(eta2_1)/(1+exp(eta2_1));
eta2_2 = c02 + c1*time + c2*group;
pm2_2=exp(eta2_2)/(1+exp(eta2_2));
eta2_3 = c03 + c1*time + c2*group;
pm2_3=exp(eta2_3)/(1+exp(eta2_3));
delta2_1 = sqrt(1+(sig2*sig2)) * probit((1/nu2)*pm2_1);
```

```
delta2_2 = sqrt(1+(sig2*sig2)) * probit((1/nu2)*pm2_2);
delta2_3 = sqrt(1+(sig2*sig2)) * probit((1/nu2)*pm2_3);
  p5=nu2 * probnorm(delta2_1 + u2);
  p6=(nu2 * probnorm(delta2_2 + u2))- (nu2 * probnorm(delta2_1 + u2));
  p7=(nu2 * probnorm(delta2_3 + u2))- (nu2 * probnorm(delta2_2 + u2));
  p8=1- (nu2 * probnorm(delta2_3 + u2));

array prob1 {4} p1-p4;
y1 = rand(''Table", of prob1[*]);
array prob2 {4} p5-p8;
y2 = rand(''Table", of prob2[*]);
  output;
end;
end;
end;

data sim;
set sim;
run;
```

Appendix 4

SAS code for fitting univariate and bivariate marginalized random-effects models with and without overdispersion parameter.

Appendix 4.1

SAS code for independence overdispersed marginalized random-effects model (the proposed OMRE model in Section 2.1)

```
proc nlmixed data=SSc qpoints=50 noad;
parms a1=-1.93 a2=1.38 a3=4.32 ta=0.14 a_sex=0.1 q1=5.36
    b1=0.54 b2=3.07 b3=4.65 b4=5.8 tb=-1 b_sex=1.1 q2=8.3
    s1=2.4 s2=1.7;
*y1=SS;
if j in (1,2,3) then do;
  nu1=exp(q1)/(1+exp(q1));
  eta1 = ta*time + a_sex*sex;
  delta11= sqrt(1+s1**2) * PROBIT( (1/nu1) * exp(a1+eta1)/(1+exp(a1+eta1)));
  delta12= sqrt(1+s1**2) * PROBIT( (1/nu1) * exp(a2+eta1)/(1+exp(a2+eta1)));
  delta13= sqrt(1+s1**2) * PROBIT( (1/nu1) * exp(a3+eta1)/(1+exp(a3+eta1)));
    if ordinal = 0 then do;
    lik = nu1*PROBNORM(delta11+u1);
    end;
    if ordinal = 1 then do;
    lik = nu1*PROBNORM(delta12+u1) - nu1*PROBNORM(delta11+u1);
    end;
    if ordinal = 2 then do;
    lik = nu1*PROBNORM(delta13+u1) - nu1*PROBNORM(delta12+u1);
    end;
    if ordinal = 3 then do;
    lik = 1 - nu1*PROBNORM(delta13+u1);
    end;
  if (lik > 1e-10) then loglik = log(lik);
   else loglik = -1e100;
end;
```

```
*y2=GS;
if j in (4,5,6) then do;
  nu2=exp(q2)/(1+exp(q2));
  eta2 = tb*time + b_sex*sex;
  delta21= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b1+eta2)/(1+exp(b1+eta2)));
  delta22= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b2+eta2)/(1+exp(b2+eta2)));
  delta23= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b3+eta2)/(1+exp(b3+eta2)));
  delta24= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b4+eta2)/(1+exp(b4+eta2)));
    if ordinal = 0 then do;
    lik = nu2*PROBNORM(delta21+u2);
    end;
    if ordinal = 1 then do;
    lik = nu2*PROBNORM(delta22+u2) - nu2*PROBNORM(delta21+u2);
    end;
    if ordinal = 2 then do;
    lik = nu2*PROBNORM(delta23+u2) - nu2*PROBNORM(delta22+u2);
    end;
    if ordinal = 3 then do;
    lik = nu2*PROBNORM(delta24+u2) - nu2*PROBNORM(delta23+u2);
    end;
    if ordinal = 4 then do;
    lik = 1 - nu2*PROBNORM(delta24+u2);
    end;
  if (lik > 1e-10) then loglik = log(lik);
     else loglik = -1e100;
end;
model ordinal ~ general(loglik);
random u1 u2 ~ normal ([0,0] , [s1**2,0,s2**2]) subject=id;
run;
```

Appendix 4.2

SAS code for joint overdispersed marginalized random-effects model (the proposed JOMRE model in Section 2.2).

```
proc nlmixed data=SSc qpoints=50 noad;
parms a1=-1.93 a2=1.38 a3=4.32 ta=0.14 a_sex=0.1 q1=5.36
    b1=0.54 b2=3.07 b3=4.65 b4=5.8 tb=-1 b_sex=1.1 q2=8.3
    s1=2.4 s12=1 s2=1.7;
*y1=SS;
if j in (1,2,3) then do;
  nu1=exp(q1)/(1+exp(q1));
  eta1 = ta*time + a_sex*sex;
  delta11= sqrt(1+s1**2) * PROBIT( (1/nu1) * exp(a1+eta1)/(1+exp(a1+eta1)));
  delta12= sqrt(1+s1**2) * PROBIT( (1/nu1) * exp(a2+eta1)/(1+exp(a2+eta1)));
  delta13= sqrt(1+s1**2) * PROBIT( (1/nu1) * exp(a3+eta1)/(1+exp(a3+eta1)));
    if ordinal = 0 then do;
    lik = nu1*PROBNORM(delta11+u1);
    end;
    if ordinal = 1 then do;
    lik = nu1*PROBNORM(delta12+u1) - nu1*PROBNORM(delta11+u1);
    end;
    if ordinal = 2 then do;
    lik = nu1*PROBNORM(delta13+u1) - nu1*PROBNORM(delta12+u1);
    end;
    if ordinal = 3 then do;
    lik = 1 - nu1*PROBNORM(delta13+u1);
```

```
      end;
    if (lik > 1e-10) then loglik = log(lik);
      else loglik = -1e100;
  end;
  *y2=GS;
  if j in (4,5,6) then do;
    nu2=exp(q2)/(1+exp(q2));
    eta2 = tb*time + b_sex*sex;
    delta21= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b1+eta2)/(1+exp(b1+eta2)));
    delta22= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b2+eta2)/(1+exp(b2+eta2)));
    delta23= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b3+eta2)/(1+exp(b3+eta2)));
    delta24= sqrt(1+s2**2) * PROBIT( (1/nu2) * exp(b4+eta2)/(1+exp(b4+eta2)));
      if ordinal = 0 then do;
      lik = nu2*PROBNORM(delta21+u2);
      end;
      if ordinal = 1 then do;
      lik = nu2*PROBNORM(delta22+u2) - nu2*PROBNORM(delta21+u2);
      end;
      if ordinal = 2 then do;
      lik = nu2*PROBNORM(delta23+u2) - nu2*PROBNORM(delta22+u2);
      end;
      if ordinal = 3 then do;
      lik = nu2*PROBNORM(delta24+u2) - nu2*PROBNORM(delta23+u2);
      end;
      if ordinal = 4 then do;
      lik = 1 - nu2*PROBNORM(delta24+u2);
      end;
    if (lik > 1e-10) then loglik = log(lik);
    else loglik = -1e100;
  end;
  model ordinal ~ general(loglik);
  random u1 u2 ~ normal ([0,0] , [s1**2,s12,s2**2]) subject=id;
  estimate ''Rho'' s12/(s1*s2);
  run;
```

Appendix 4.3

SAS code for joint marginalized random-effects model (the JMRE model without an overdispersion).

```
  proc nlmixed data=SSc qpoints=50 noad;
  parms a1=-1.93 a2=1.38 a3=4.32 ta=0.14 a_sex=0.1
      b1=0.54 b2=3.07 b3=4.65 b4=5.8 tb=-1 b_sex=1.1
      s1=2.4 s12=1 s2=1.7;
  *y1=SS;
  if j in (1,2,3) then do;
    eta1 = ta*time + a_sex*sex;
    delta11= sqrt(1+s1**2) * PROBIT( exp(a1+eta1)/(1+exp(a1+eta1)));
    delta12= sqrt(1+s1**2) * PROBIT( exp(a2+eta1)/(1+exp(a2+eta1)));
    delta13= sqrt(1+s1**2) * PROBIT( exp(a3+eta1)/(1+exp(a3+eta1)));
      if ordinal = 0 then do;
      lik = PROBNORM(delta11+u1);
      end;
      if ordinal = 1 then do;
      lik = PROBNORM(delta12+u1) - PROBNORM(delta11+u1);
      end;
      if ordinal = 2 then do;
```

```
    lik = PROBNORM(delta13+u1) - PROBNORM(delta12+u1);
    end;
    if ordinal = 3 then do;
    lik = 1 - PROBNORM(delta13+u1);
    end;
  if (lik > 1e-10) then loglik = log(lik);
   else loglik = -1e100;
end;
*y2=GS;
if j in (4,5,6) then do;
  eta2 = tb*time + b_sex*sex;
  delta21= sqrt(1+s2**2) * PROBIT( exp(b1+eta2)/(1+exp(b1+eta2)));
  delta22= sqrt(1+s2**2) * PROBIT( exp(b2+eta2)/(1+exp(b2+eta2)));
  delta23= sqrt(1+s2**2) * PROBIT( exp(b3+eta2)/(1+exp(b3+eta2)));
  delta24= sqrt(1+s2**2) * PROBIT( exp(b4+eta2)/(1+exp(b4+eta2)));
    if ordinal = 0 then do;
    lik = PROBNORM(delta21+u2);
    end;
    if ordinal = 1 then do;
    lik = PROBNORM(delta22+u2) - PROBNORM(delta21+u2);
    end;
    if ordinal = 2 then do;
    lik = PROBNORM(delta23+u2) - PROBNORM(delta22+u2);
    end;
    if ordinal = 3 then do;
    lik = PROBNORM(delta24+u2) - PROBNORM(delta23+u2);
    end;
    if ordinal = 4 then do;
    lik = 1 - PROBNORM(delta24+u2);
    end;
  if (lik > 1e-10) then loglik = log(lik);
   else loglik = -1e100;
end;
model ordinal ~ general(loglik);
random u1 u2 ~ normal ([0,0] , [s1**2,s12,s2**2]) subject=id;
estimate ''Rho'' s12/(s1*s2);
run;
```