Multivariate Analysis of Longitudinal Rates of Change: Supplementary Materials

This document provides additional results for assessing the power of the Multivariate Longitudinal Rate Regression model (MLRR) under a Global Multivariate Proportional Rate (GMPR) assumption compared to an unconstrained MLRR model with separate rate estimates for each outcome, and a pre-selected univariate Longitudinal Rate Regression (LRR) model for a single outcome in scenarios with varying levels of violation of the GMPR assumption. The set up for these calculation for a trivariate outcome is described in detail in the main manuscript.

1 Multivariate Power Under Increased Across Outcome Correlation

The following calculations replicate those from the main manuscript with an altered correlation structure in order to illustrate the potential impact of changes in the covariance structure on the power of the two multivariate approaches. The primary change in the correlation structure was to increase the across outcome random effect correlation. The correlation between intercept and slope random effects within an outcome was also reduced in order to ensure the specification of a positive definite covariance matrix. Hence, the following covariance structure was used for these calculations:

$$\mathbf{R} = \begin{pmatrix} 1.000 & 0.016 & 0.750 & 0.003 & 0.750 & 0.003 \\ 0.016 & 0.100 & 0.003 & 0.075 & 0.003 & 0.075 \\ 0.750 & 0.003 & 1.000 & 0.016 & 0.750 & 0.003 \\ 0.003 & 0.075 & 0.016 & 0.100 & 0.003 & 0.075 \\ 0.750 & 0.003 & 0.750 & 0.003 & 1.000 & 0.016 \\ 0.003 & 0.075 & 0.003 & 0.075 & 0.016 & 0.100 \end{pmatrix}.$$

All other specifications detailed in the main manuscript were left unchanged.

The resulting power curves from the altered covariance structure under the three scenarios are presented in Figure S1. When the GMPR assumption is correct, the global MLRR model maintains higher power relative to the univariate LRR model and joint MLRR model (see Figure S1(a)) though the advantage is less substantial compared to the curves presented in the main manuscript. In both scenarios where the GMPR assumption is violated, the global MLRR model was less powerful compared to the other two approaches (see Figure S1(b) and Figure S1(c)). Not surprisingly, these results illustrate how the power for the global MLRR model will suffer as the correlation between the measured outcomes increases. Therefore, when the outcome measures are highly correlated, the global MLRR model may only be advantageous in terms of power compared to a univariate or joint multivariate approach when the effect (difference in the rate of change due to exposure) for each outcome is the same or highly similar.

The joint MLRR model in Figure S1 displays an interestingly different behavior compared to the results presented in the primary manuscript. The power for the joint MLRR model is reduced relative to the univariate model when the rate effect is the same for each outcome (see Figure S1 (a)). The joint MLRR model likely suffers in this scenario due to the increased degrees of freedom of the joint test and an insufficient increase in information from the multivariate outcome due to the high correlation. However, as shown in panels (b) and (c), as the rate effects for the second and third outcome decrease in magnitude in the second and third scenarios, the joint MLRR model actually increases in power and surpasses the univariate model in the third scenario. Thus, this alternative calculation illustrates the complexity of examining power in a multivariate setting as it can be highly dependent on the assumed covariance structure and the direction of the alternative.

Although the positive behavior of the joint MLRR model may appear surprising, the result can be explained by the impact of correlation on relative power when considering different alternative structures (directions) with multivariate statistics, and by the mathematical structure of the MLRR model. First, even in relatively simple settings such as with MANOVA, Cole et al. [1] discuss apparent contradictions where power may actually increase using multivariate testing when the correlation increases among outcomes that have different effect sizes, and this can explain the results for MLRR in panel (b) relative to panel (a). Second, the displayed behavior may be explained by two structural factors: the underlying relationship between the rate effect size and its asymptotic standard error induced by the interaction between the reference time structure and the rate structure, and the increased correlation between the random slope effects across outcomes. The basic form of the relationship between the rate effect and its standard error can be discerned by considering the derivative of the mean structure for the MLRR model with respect to parameters of the reference time function. For example, if we set our reference function for the kth outcome $\mu_{0k}(t_{ijk}) = \boldsymbol{\beta}_k' \mathbf{T}_{ijk}$ and take the derivative of Equation (2) from the main manuscript with respect to parameter β_{kl} (the coefficient for basis function l of the kth outcome), we obtain the following results:

$$\frac{\partial E(Y_{ijk} \mid \mathbf{X}_i = \mathbf{x}, t_{ij} = t)}{\partial \beta_{kl}} = (1 + \boldsymbol{\theta}_k \mathbf{x})\mathbf{T}_{\cdot\cdot k}.$$

For the above derivative, we did not impose the GMPR assumption since these calculations correspond to the joint MLRR model. The important result of the above derivation is that the derivative of the mean structure with respect to parameters in the reference function will depend on the value of the rate paremeter. As outlined in the appendix to the main manuscript, the hessian equation for the cross component of the rate parameter and reference time function parameter will depend on the above derivative. Furthermore, the standard error of the rate parameter can be expressed as a function of the hessian matrix can be expressed as follows:

$$\mathrm{Var}(\hat{\theta_k}) = [H_{11} - H_{12}H_{22}^{-1}H_{21}]^{-1}$$

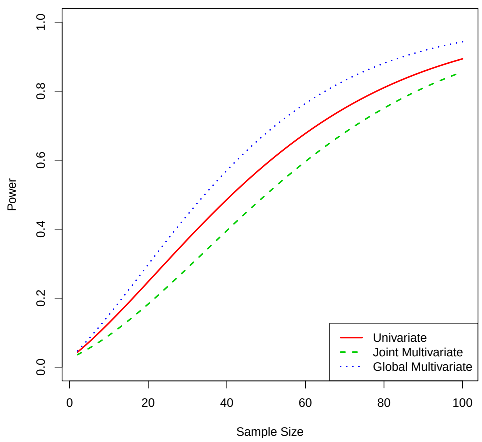
where H_{11} denotes the hessian components for the rate parameter, H_{22} denotes the hessian components for all other parameters, and H_{12} and H_{21} denote the hessian for the cross components of the rate parameter and all other parameters. Therefore, since the cross components matrices H_{12} and H_{21} depend on the rate structure based on the above calculation, the standard error for the rate parameter will also depend on the rate structure in the form of the inverse of a function that has negative quadratic form with respect to the rate structure. Thus, the standard error of the rate parameter will have a u-shaped relationship with the value of the rate parameter with a minimum standard error when the rate parameter is equal to -1.

Note that these calculations are provided in the context of the joint MLRR model, but this relationship between the rate parameter and its standard error will also exist in the univariate LRR model and the MLRR model with a globally estimated rate parameter. Results from this manuscript suggest that the power curves for the latter two models consistently increase with respect to effect size suggesting that the effect size as it relates to power grows at a faster rate than the standard error for these models. This also seems to be the case for the joint MLRR model when the measured outcomes are mildly correlated. The results presented in this document shows that this relationship no longer holds for the joint MLRR model when the outcomes are strongly correlated. A more detailed assessment (results not shown) conveys that power for this test as the rate effect for the second and third outcome decrease toward zero is u-shaped. This result suggests that the increased correlation reduces the total variation such that the size of the standard error of the rate parameters drive the power. Further exploration indicates that this u-shaped behavior only occurs when the correlation between random slope effects across outcomes is increased and is not impacted by other increased correlations. The importance of the correlation in random slopes is likely due to the interaction between the random slope and the reference time function in the model. From an intuitive stand point, the behavior may be explained by the diverging rate effects for each outcomes. As the rate effects for the three outcome become less similar, the imposed strong correlation across outcome may force a reduction in the total variation in order for this strong across outcome correlation to be consistent with the increasingly diverse behavior in the rate structure. Such intuition would be consistent with the results presented by Cole et al. [**?**] and might suggest that the increased across outcome correlation is the primary factor for explaining the increased power with diverging effect size. Further exploration is need to examine this possibility as well as other consequences of altering the covariance structure of this model.

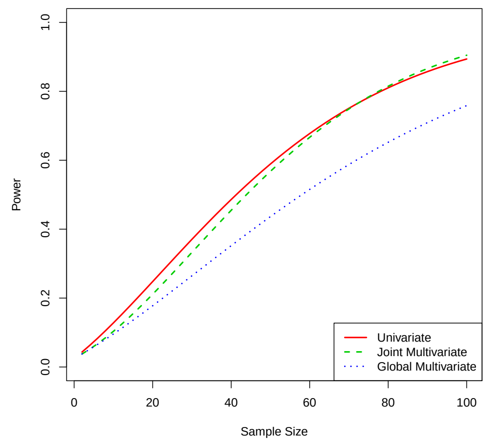
References

[1] Cole D, Maxwell S, Arvey R, Salas E. How the power of MANOVA can both increase and decrease as a function of the intercorrelations among the dependent variables. *Quantitative Methods in Psychology* 1994; **115**:465–474. DOI: 10.1037//0033-2909.115.3.465.

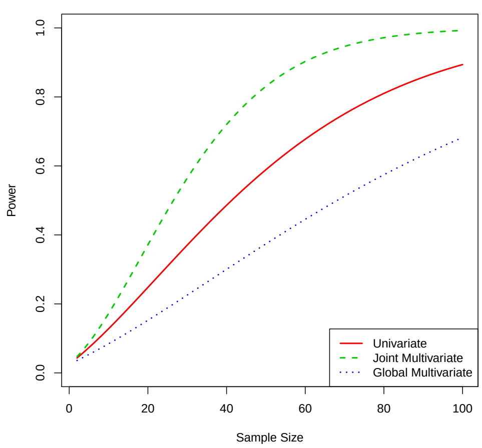
Figure S1



(a)



(b)



(c)

Power curves for testing group differences in the rate of change for three outcomes between two groups for the univariate LRR model (solid red), the MLRR model with separate rate parameters for each outcome (dashed green), and the MLRR model with a global rate parameter (dotted blue). **(a)** The true data was generated from a model where the rate parameter for each outcome was the same and the GMPR assumption was correct. The global rate effect size is 25%. **(b)** The true data was generated from a model where the rate parameters for the second and third outcomes respectively were two-thirds and one-third the size of the rate parameter for the first outcome. The rate effect sizes for the each outcome was 25%, 16.7%, and 8.3%. **(c)** The true rate parameter for the second and third outcomes respectively were reduced by half and to zero relative to the rate parameter of the first outcome. The rate effect sizes for each outcome was 25%, 12.5%, and 0%. The power curve for the univariate LRR model was generated from testing the first outcome whose rate effect was 25% in each scenario.