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Sample size and power calculations for correlations between bivariate longitudinal data

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Abstract

The analysis of a baseline predictor with a longitudinally measured outcome is well established and sample size calculations are reasonably well understood. Analysis of bivariate longitudinally measured outcomes is gaining in popularity and methods to address design issues are required. The focus in a random effects model for bivariate longitudinal outcomes is on the correlations that arise between the random effects and between the bivariate residuals. In the bivariate random effects model, we estimate the asymptotic variances of the correlations and we propose power calculations for testing and estimating the correlations. We compare asymptotic variance estimates to variance estimates obtained from simulation studies and compare our proposed power calculations for correlations on bivariate longitudinal data to power calculations for correlations on cross-sectional data.

Keywords

power analysis; bivariate longitudinal design; repeated measures; correlation

1. Introduction

The use of bivariate longitudinal modeling has outpaced the development of sample size and power calculations for bivariate longitudinal study designs. Analysis of bivariate and multivariate longitudinal data [1–4] is now practical with the development of appropriate algorithms implemented in statistical software, for example MPLUS [5], the PROC GLIMMIX, MIXED, and NLMIXED procedures in SAS [6], the sabreR package in R [7], and WinBUGS [8]. See Appendix A for an example using the PROC MIXED procedure. Bivariate longitudinal models have gained in popularity across numerous research fields including HIV immunology [9], smoking progression and physical activity in public health [10], and sexual behavior related to HIV transmission [11].

Meanwhile, methodology [12–14] and software packages, such as RMASS2 [14] and PASS [15], to perform longitudinal power calculations target the relationship between a univariate longitudinal outcome and a scalar covariate. In a grant proposal, analyses on longitudinal bivariate relationships are historically treated as secondary analyses that do not require power calculations.

As the exploration of bivariate longitudinal relationships takes center stage, appropriate power calculations are needed. The focus of a bivariate longitudinal analysis is on the correlations between outcomes over time [16, 17]. A non-model-based approach is to estimate the Pearson product-moment correlation and variance of the correlation, either using the asymptotic normal distribution or theory of U -statistics; a one-sample z -test framework is used to calculate power [18, 19]. This approach can be used to test for changes in correlations between repeated observations or test for differences between pairs of outcomes in a cluster study design. However, if modeling assumptions can be made about the correlations, a model-based approach offers greater efficiency. For example, if equal correlations are assumed across time points, perhaps the most popular model for bivariate longitudinal data is the bivariate random intercept model [20, 21] [4, Chapter 13]. Adjustment covariates can be included in the model to further improve efficiency, which cannot be done using a non-model-based approach. We consider a bivariate model with a random intercept for each outcome and correlated residuals within time, and focus on two types of correlations: (1) the correlation between mean levels of the two outcomes within each subject, i.e. the correlation ρ between paired random intercepts and (2) the correlation between paired outcomes at each time point within each subject conditional on the random effects, i.e. the correlation r between paired residuals. Power can also be calculated for the correlation between repeated observations on a single outcome within each subject, i.e. the intraclass correlation [22], but is typically not the focus of a bivariate analysis.

We propose power calculations for correlations on the paired outcomes of a bivariate random intercept model defined in Section 2. We determine the necessary sample size to test the null hypotheses, $H_0 : \rho = 0$ and $H_0 : r = 0$. Keen and Srivastava [23] and Tu *et al.* [18, 19] use maximum likelihood (ML) estimation to calculate the asymptotic variance of the interclass correlation coefficient for nested genetic data and to calculate the asymptotic variance of the correlation coefficient for nested or longitudinal data, respectively. In a similar manner, we use the observed Fisher information to derive the asymptotic variances for $\hat{\rho}$ and $\hat{r}$ under ML and restricted ML (REML), both for balanced data in Section 3.1 and unbalanced data in Section 3.2. We compare the asymptotic variance expressions to variances estimated from simulation studies in Section 3.3. Power calculations are formulated in Section 4 and compared to power calculations on cross-sectional data in Section 5. Discussion follows in Section 6.

2. The bivariate random intercept model

We consider a bivariate random-intercept linear model [20, 21] [4, Chapter 13]. Essentially this is the generalization of the compound symmetry covariance structure to bivariate longitudinal observations. Continuous observations y_{ijk} on subjects $i = 1, \dots, n$ are taken at n_i distinct times t_{ij} for $j = 1, \dots, n_i$ for each subject for outcome $k = 1, 2$. Except in Sections 3.2 and 3.4, we assume balanced data $n_i \equiv J$ for all subjects.

Observations y_{ijk} are modeled as

$$y_{ijk} = x'_{ijk}\alpha_k + z'_{ijk}\beta_i + \varepsilon_{ijk}, \quad (1)$$

where α_k is a vector of regression coefficients for response $k = 1$ or 2 on covariate vector x_{ijk} ; $z_{ij1} \equiv (1, 0)'$ and $z_{ij2} \equiv (0, 1)'$ for the random-intercept model, random effect vector $\beta_i = (\beta_{i1}, \beta_{i2})' \sim N_2(0, T)$, and residual vector $\varepsilon_{ij} = (\varepsilon_{ij1}, \varepsilon_{ij2})' \sim N_2(0, \Sigma)$. Residual vectors from different times or different subjects are independent of each other and independent of the random effects vectors. Random effects from different subjects are independent. The random effect covariance matrix is

$$T = \begin{pmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{pmatrix}, \quad (2)$$

and the residual covariance matrix is

$$\Sigma = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}, \quad (3)$$

where $\tau_{12} = \rho\tau_1\tau_2$ and $\sigma_{12} = r\sigma_1\sigma_2$ are the covariances corresponding to the correlations ρ and r of interest.

Define $\mathbf{1}$ as a column vector of ones and $\mathbf{0}$ as a column vector of zeros, both of length J , and let

$$Z = \begin{pmatrix} \mathbf{1} & \mathbf{0} \\ \mathbf{0} & \mathbf{1} \end{pmatrix}. \quad (4)$$

Define block diagonal covariate matrix $X_i = I_2 \otimes X_{i1}$, with $2J$ rows and I_2 is a 2×2 identity matrix, X_{i1} is a matrix with J rows of covariate vectors X'_{ij1} for subject i assumed for notational convenience to be the same for both outcome variables, and $A \otimes B = (a_{jk} B)$ is the Kronecker product of matrices A and B with jk th block $a_{jk} B$. The distribution of response vector $Y_i = (y_{i11}, \dots, y_{iJ1}, y_{i12}, \dots, y_{iJ2})'$ is $Y_i \sim N_{2J}(X_{i\alpha}, V)$ with mean vector $X_{i\alpha}$ where $\alpha = (\alpha'_1, \alpha'_2)'$ and covariance matrix

$$V = ZTZ' + \Sigma \otimes I_J, \quad (5)$$

where I_J is a $J \times J$ identity matrix. The variance parameters are $\theta = (\tau_1, \tau_2, \rho, \sigma_1, \sigma_2, r)'$. The log-likelihood as a function of (α, θ) given the data is

$$\log \ell(\alpha, \theta | Y)_{\text{ML}} \propto -\frac{n}{2} \log |V| - \frac{1}{2} \text{tr}[S^* V^{-1}]. \quad (6)$$

The residual sums of squares matrix is

$$S^* = \left[\sum_{i=1}^n (Y_i - X_i \alpha)(Y_i - X_i \alpha)' \right] \quad (7)$$

and is a function of α . We substitute $\hat{\alpha} \equiv \hat{\alpha}(V) = (\sum_i X'_i V^{-1} X_i)^{-1} \sum_i (X'_i V^{-1} Y_i)$ into (7) and get $S = S^*|_{\alpha=\hat{\alpha}}$. The goal of the eventual analysis is to estimate ρ and r . The goal of our paper is to choose an appropriate sample size that will allow us to accurately estimate ρ and r .

3. Asymptotic variances of the correlation estimates

3.1. Derivation of the correlation variances for balanced data

The asymptotic variances of parameters (α, θ) are the diagonal elements of $I(\alpha, \theta)^{-1}$, the inverse of the information matrix

$$I(\alpha, \theta) = -E \left[\frac{\partial^2 \log \ell(\alpha, \theta | Y)}{\partial(\alpha, \theta) \partial(\alpha, \theta)'} \right], \quad (8)$$

which we partition as

$$I(\alpha, \theta) = \begin{pmatrix} I_{\alpha, \alpha} & I_{\alpha, \theta} \\ I_{\theta, \alpha} & I_{\theta, \theta} \end{pmatrix}. \quad (9)$$

The cross-term $I_{\alpha, \theta} = 0$ [24, 25], therefore we only need to consider $I_{\theta, \theta}$ to obtain variances of the correlation estimates. Under ML estimation, the (r, s) element of the Fisher Information matrix $I_{\theta, \theta}$ is [24, 26, 27]

$$I_{\theta, \theta}(r, s) = \frac{n}{2} \Lambda(r, s) \quad (10)$$

and

$$\Lambda(r, s) = \text{tr} \left(V^{-1} \frac{\partial(V)}{\partial \theta_r} V^{-1} \frac{\partial(V)}{\partial \theta_s} \right). \quad (11)$$

In Appendix B, we simplify V^{-1} into a form that is easier to incorporate into numerical calculations.

REML estimation subtracts $\frac{1}{2} \sum_{i=1}^n \log |X_i' V^{-1} X_i|$ from the log-likelihood in (6) as a correction factor [28, Appendix 1]; the Fisher Information matrix $I_{\theta, \theta}$ is dependent on covariate matrix X_i . Under REML estimation, the (r, s) element of the Fisher Information matrix $I_{\theta, \theta}$ is

$$I_{\theta, \theta}(r, s) = \frac{n}{2} \left(\Lambda(r, s) + \frac{1}{n} \Xi(r, s) \right) \quad (12)$$

and

$$\Xi(r, s) = \left(\frac{\partial^2 \left(\sum_{i=1}^n \log |X_i' V^{-1} X_i| \right)}{\partial \theta_r \partial \theta_s} \right). \quad (13)$$

Power calculations on correlations ρ and r typically consider a simple covariate matrix. For a bivariate random intercept model, it is reasonable to consider an intercept only model, where $x_{ij1} = (1, 0)'$ and $x_{ij2} = (0, 1)'$. There is a population mean for each outcome that is time-fixed and the same across subjects, $X_i \equiv X$. The bivariate random intercept model for the covariance structure means that each subject's mean for each outcome is also time-fixed but may differ from the population mean. For the intercept only model, $(X' V^{-1} X)^{-1}$ simplifies into a form that is easier to incorporate into numerical calculations; see Appendix C. In Appendix D, expression (13) is expanded so that derivatives are only taken on V and not $\sum_{i=1}^n \log |X_i' V^{-1} X_i|$. We then partition $\theta = (\theta_1, \theta_2)$, where $\theta_1 = (\tau_1, \tau_2, \rho)'$ and $\theta_2 = (\sigma_1, \sigma_2)$,

r)' to formulate the inverse of $I_{\theta,\theta}(r, s)$ in terms of submatrices that are easier to invert [29, p. 390]. The asymptotic variances of the correlation parameter ρ between paired random intercepts and correlation r between paired residuals are the (3,3) and (6,6) elements respectively of the inverted information matrix,

$$\text{Var}(\hat{\rho}) = I_{\theta,\theta}^{-1}(3, 3) \quad (14)$$

and

$$\text{Var}(\hat{r}) = I_{\theta,\theta}^{-1}(6, 6). \quad (15)$$

We use the symbolic computation program Maple version 12 (Waterloo Maple 2008 [30]) to derive expressions for the variances of correlation $\hat{\rho}$ and $\hat{r}$ using (14) and (15), respectively. Under the assumption of a bivariate random intercept model with a compound symmetry covariance structure, the ML variance of correlation $\hat{r}$ between paired residuals simplifies nicely to

$$\text{Var}(\hat{r}) = \frac{(1 - r^2)^2}{n(J - 1)}. \quad (16)$$

For n subjects, $\text{Var}(\hat{r})$ is only dependent on r and the number of repeated observations J . This is the same as the asymptotic variance of a Pearson product-moment correlation coefficient $\hat{\gamma}$ between $m = n(J - 1)$ independent pairs of observations from a bivariate normal distribution with population correlation coefficient γ [31, p. 30],

$$\text{Var}(\hat{\gamma}) = \frac{(1 - \gamma^2)^2}{m}. \quad (17)$$

Some texts give the denominator of $\text{Var}(\hat{\gamma})$ as $m - 2$ [32, p. 221], [33, p. 556].

Unlike the ML variance expression for correlation ($\hat{r}$) in (16), the ML variance of correlation $\hat{\rho}$ between paired random intercepts, $\text{Var}(\hat{\rho})$, as well as the REML variances of $\hat{\rho}$ and $\hat{r}$, do not reduce to simple expressions. Instead we calculate the variances directly from equations (14) and (15) in R version 2.4.1 [7]. We explore the relationship between covariance parameter values and correlation variances for differing combinations of covariance matrix parameter values. Empirical results for $\text{Var}(\hat{\rho})$ are summarized in Table I for $n = 50$ and $J = 4$. Empirical results for $\text{Var}(\hat{r})$ are not shown. The ML $\text{Var}(\hat{r})$ does not change for differing covariance parameter values, other than r ; changes in REML $\text{Var}(\hat{r})$ are negligible. For example, REML $\text{Var}(\hat{r})$ for $\hat{r} = 0.2$ and differing values of τ_1 , τ_2 , σ_1 , σ_2 , and ρ from Table I are limited to a range of 0.006139 to 0.006143. Furthermore, empirical results show that if both ρ and r are set to zero, the typical correlation values for a null hypothesis, then REML $\text{Var}(\hat{r})$ reduces to $1/(n(J - 1))$, the ML $\text{Var}(\hat{r})$ estimate in (16) when $r = 0$.

Empirically observed rules are listed in Table II for the direction of the relationships between the covariance parameters and the resulting asymptotic variances of the two correlation parameters. ML and REML $\text{Var}(\hat{\rho})$ are invariant to τ_1^2/σ_1^2 and τ_2^2/σ_2^2 . ML and REML $\text{Var}(\hat{\rho})$ decrease with: (a) increasing $|\rho|$, (b) increasing r in value from -1 to 1 , (c) increasing τ_1^2 or τ_2^2 , and (d) decreasing σ_1^2 or σ_2^2 . ML and REML $\text{Var}(\hat{r})$ decreases with

increasing $|r|$. REML $\text{Var}(\hat{\rho})$ decreases with: (a) increasing ρ in value from -1 to 1 , (b) increasing σ_1^2 or σ_2^2 and (c) decreasing τ_1^2 or τ_2^2 .

While a bivariate regression analysis typically focuses on the components of variance that contribute to correlations across outcomes, our proposed methods are applicable to power calculations on the marginal correlation. For bivariate observations, the *marginal concurrent correlation* ϱ_{jj} between y_{ij1} and y_{ij2} , is

$$\varrho_{jj} = (\tau_{12} + \sigma_{12}) / \sqrt{(\tau_1^2 + \sigma_1^2)(\tau_2^2 + \sigma_2^2)} \quad (18)$$

and is a mixture of ρ and r . If $cT = \Sigma$, then $\varrho = \rho = r$. In general $\varrho_{jj}^2 \leq \max(\rho^2, r^2)$. A special case is of interest. Suppose that $\tau_1^2 = c\sigma_1^2$ and $\tau_2^2 = c\sigma_2^2$. Note that this implies that $\tau_1^2 = c^* \tau_2^2$ and $\sigma_1^2 = c^* \sigma_2^2$ as might happen if y_{ij1} and y_{ij2} were themselves repeated measures. Then $\varrho = (\tau_1^2 r + \sigma_1^2 \rho) / (\tau_1^2 + \sigma_1^2)$ is a convex combination of ρ and r . If it should happen that $\rho = -r\tau_1\tau_2\sigma_1^{-1}\sigma_2^{-1}$, then $\varrho \equiv 0$. For $j \neq j'$, the *marginal lagged correlation* between y_{ij1} and $y_{ij'2}$, is

$$\varrho_{jj'} = \tau_{12} / \sqrt{(\tau_1^2 + \sigma_1^2)(\tau_2^2 + \sigma_2^2)}. \quad (19)$$

The expressions for ρ and $\varrho_{jj'}$ have the same numerator, but the denominator for $\varrho_{jj'}$ is greater than or equal to the denominator for ρ . Therefore, $\varrho_{jj'}^2 \leq \rho^2$. By applying the delta method [34, p. 149], the variance of $\varrho_{jj'}$ for $j = j'$ and $j \neq j'$ is estimated as

$$\text{Var}(\hat{\varrho}_{jj'}) = D' I_{\theta, \theta}^{-1} D, \quad D = \partial(\varrho_{jj'}) / \partial(\theta). \quad (20)$$

Expressions for the partial derivatives of ϱ with respect to the variance parameters θ are given in Appendix E.

3.2. Derivation of the correlation variances for unbalanced data

For the bivariate random-intercept linear model, it is convenient to view unbalanced data, e.g. data with missing observations, as a collection of data subsets s , $s = 1, \dots, M$. Data

subset s has m_s subjects, $\sum_{s=1}^M m_s = n$, each with the same number of repeated observations. M is less than or equal to the maximum number of observations on a subject. Because of the exchangeability of the n_i repeated observations under the random intercept covariance model, the contribution to the calculations of the various missing data patterns depends only on the number of repeated observations n_i , and not on the full temporal missingness pattern. The Fisher Information for the entire data set is the sum of the Fisher Information matrices

for each data subset $I_{\theta, \theta}(s)$, $I_{\theta, \theta} = \sum_{s=1}^M I_{\theta, \theta}(s)$ and the variance is obtained by inverting $I_{\theta, \theta}$.

3.3. Variance simulation studies for balanced data

We compare asymptotic correlation variances calculated directly from equations (14) and (15) to correlation variances estimated by simulation. Simulations are carried out in SAS software version 9.1 [6]. We generate multivariate normally distributed random variates, $Y_i^{(\ell)} \sim N(\mathbf{0}, V)$, $i=1, \dots, n$, using the PROC IML procedure, where V is covariance matrix (5).

From the $Y_i^{(\ell)}$, we construct 81 sets of 100 data sets with $n = 10, 50$, or 250 , $J = 2, 4$, or 6 , and for each of nine possible sets of correlations from setting $\rho = 0.2, 0.5$, or 0.8 and setting $r = 0.2, 0.5$, or 0.8 . We set an intercept only model where $x_{ij1} = (1, 0)'$ and $x_{ij2} = (0, 1)'$ and the fixed effect parameter values are $\alpha = (0, 0)'$. We set variance parameter values,

$\tau_1^2=1, \tau_2^2=3, \sigma_1^2=1$, and $\sigma_2^2=2$, to values similar to estimates from studies at our center. For example, the following variances were estimated in a longitudinal bivariate analysis of the Beck Depression Inventory [35], after a square root transformation, and the number of days using drugs other than alcohol or marijuana, after a log base 2 transformation [36]:

$\hat{\tau}_{BDI}^2=1.04, \hat{\tau}_{drugs}^2=2.54, \hat{\tau}_{BDI}^2=0.77$, and $\hat{\tau}_{drugs}^2=1.91$. For each combination of n, J , and correlation parameters, ρ and r , we fit the bivariate random-intercept linear regression model (1) with bivariate random intercept covariance structure to the ℓ th data set and collect $\hat{\rho}^{(\ell)}$ and $\hat{r}^{(\ell)}$.

Models are fit using both ML and REML estimation through the PROC MIXED procedure. Correlation variances for each simulation study are calculated as

$\text{Var}(\hat{\rho}) = \sum_1^L (\hat{\rho}^{(\ell)} - \bar{\rho})^2 / L$ and $\text{Var}(\hat{r}) = \sum_1^L (\hat{r}^{(\ell)} - \bar{r})^2 / L$, where $\bar{\rho}$ and $\bar{r}$ are means of the $\hat{\rho}^{(\ell)}$ and $\hat{r}^{(\ell)}$, respectively. The standard deviation (SD) is the square root of the variance.

Prior to comparing asymptotic and simulated correlation variances, we conduct diagnostic tests to check for systematic problems in estimating correlation variances from our simulations. The bias is estimated for ρ as

$$\text{bias}_\rho = \bar{\rho} - \rho \quad (21)$$

[34, Chapter 4] and the mean squared error (MSE) for ρ is $\text{Var}(\hat{\rho}) + \text{bias}_\rho^2$, estimated by

$\sum_1^L (\hat{\rho}^{(\ell)} - \rho)^2 / L$, and similarly for r ; ML results are shown for $n = 250$ and $J = 4$ repeated measurements in Table III.

Across the 81 simulation studies, i.e. 27 simulation studies for each of three sample sizes, biases were relatively small and similar between ML and REML correlation estimates. For both ML and REML, simulation results estimated the absolute value of the bias to be approximately 1/10 the size of the SD. For ML and REML estimations of ρ , means of the absolute bias to SD ratios are 0.12, 0.11, and 0.07 for $n = 10, 50$, and 250 , respectively. For ML and REML estimates of r , means of the absolute bias to SD ratios are 0.10, 0.05, and 0.07 for $n = 10, 50$, and 250 , respectively. More formally, we conduct two-sided t -tests to test the null hypothesis that the biases are zero. For ρ , $t = \sqrt{L} \text{bias}_\rho / \sqrt{\text{Var}(\hat{\rho})}$, and for r , $t = \sqrt{L} \text{bias}_r / \sqrt{\text{Var}(\hat{r})}$. Across the 81 ML simulation studies, p -values for ρ and r were less than 0.05 for 12 (15 per cent) and 4 (5 per cent) simulation studies respectively. Across the 81 REML simulation studies, p -values for ρ and r were less than 0.05 for 10 (12 per cent) and 3 (4 per cent) simulation studies, respectively. Six of the 12 significant ML results for ρ occurred for $n = 10$; REML results for ρ were more evenly spread between $n = 10, 50$, and 250 . All of the significant ML and REML results for r occurred for $n = 10$. The directions of the bias were fairly evenly split between positive and negative values for both ρ and r . An exception occurred for ρ with $n = 10$, where only 5 of 27 biases for ML ρ estimates and 5 of 27 biases for REML ρ estimates were positive. We conclude that random intercept correlation estimates are biased towards zero for small n .

Scatterplots for ML simulations conducted in SAS versus ML asymptotic calculations are shown for $\text{Var}(\hat{\rho})$ in Figure 1 and $\text{Var}(\hat{r})$ in Figure 2. For $n = 10$, asymptotic calculations on

$\text{Var}(\hat{\rho})$ tend to be less than simulations, indicating that the asymptotic calculations are less conservative. Even for $J = 4$ or $J = 6$ the formulas are fairly accurate. For $J = 2$ and $n = 50$, $\text{Var}(\hat{\rho})$ is slightly less conservative. For $\text{Var}(\hat{r})$, only for $J = 2$, $n = 10$ and either $r = 0.5$ or $r = 0.8$ is there much of a hint the variance formula is less conservative.

3.4. Variance simulation studies for unbalanced data

Following the same simulation procedures to create balanced data sets, we simulated unbalanced data sets with $n = 250$ subjects. Within each data set, subjects differed on the number of repeated observations; subjects were simulated to have $J = 2, 4$, or 6 repeated observations. Table IV shows ML correlation variances for four simulated data sets. We show ML correlation variances for three balanced data sets simulated earlier for reference. ML asymptotic correlation variances for ρ and r are also displayed in Table IV. As an example, the simulated and asymptotic variances for r in the first row of Table IV are 0.0018 and 0.0016, respectively, for a data set containing 125 subjects with two repeated observations and 125 subjects with four observations. Simulation and asymptotic variances for r are close in value, as expected from results on balanced data. Theoretical variances for ρ are conservative compared to the simulated variances.

4. Power calculations

We discuss sample size and power calculations in terms of correlation ρ between paired random intercepts; calculations for correlation r between paired residuals and marginal correlations ρ_{jj} and $\rho_{jj'}$ follow in an identical manner. The null hypothesis H_0 being tested is that the true correlation ρ is a specific value ρ_0 , $H_0 : \rho = \rho_0$. Typically, $\rho_0 = 0$. The alternate hypothesis is $H_1 : \rho = \rho_1$. We assume that the variance is known and use the framework of a one-sample two-sided z -test where Z_α is the value from a standardized normal distribution that yields the desired alpha level and $\Phi(x)$ is the area under the standardized normal curve to the left of x [37, Chapter 10]. The ML equation for sample size n is

$$n_{\text{ML}} = \frac{2(Z_\alpha - Z_\beta)^2 \Lambda_{(3,3)}^{-1}|_{\rho=\rho_0}}{(\rho_0 - \rho_1)^2}, \quad (22)$$

and the equation for power is

$$\text{Power}_{\text{ML}} = 1 - \Phi \left(Z_\alpha - \sqrt{\frac{n(\rho_0 - \rho_1)^2}{2\Lambda_{(3,3)}^{-1}|_{\rho=\rho_0}}} \right). \quad (23)$$

Recalling the simplified form of ML $\text{Var}(\hat{r})$ for the correlation of paired residuals in (16), sample size and power calculations to test $H_0 : r = r_0$ reduce to

$$n_{\text{ML}_r} = \frac{(Z_\alpha - Z_\beta)^2 (1 - r_0^2)^2}{(r_0 - r_1)^2 (J - 1)}, \quad (24)$$

and the equation for power is

$$\text{Power}_{\text{ML}_r} = 1 - \Phi \left(Z_\alpha - \sqrt{\frac{n(r_0 - r_1)^2 (J - 1)}{(1 - r_0^2)^2}} \right). \quad (25)$$

Through REML estimation, the necessary sample size n_{REML} to achieve a specified power is the solution to the expression

$$(\rho_0 - \rho_1)^2 = 2(Z_\alpha - Z_\beta)^2 (n_{\text{REML}} \Lambda + \Xi)^{-1}_{(3,3)} |_{\rho=\rho_0}, \quad (26)$$

which can be found by an iterative process. The REML equation for power is

$$\text{Power}_{\text{REML}} = 1 - \Phi \left(Z_\alpha - \sqrt{\frac{(\rho_0 - \rho_1)^2}{2(n\Lambda + \Xi)^{-1}_{(3,3)} |_{\rho=\rho_0}}} \right). \quad (27)$$

5. Real data example

We illustrate our proposed power calculations on data from the Healthy Living Project (HLP), a behavioral intervention trial that was designed to reduce HIV-transmission behaviors in HIV-positive adults. After recruitment, study participants were randomized to an intervention arm, offering cognitive behavioral therapy sessions, or a control arm, offering the intervention to participants after the trial was completed. Participants in both arms completed an initial assessment and follow-up assessments at 5, 10, 15, 20, and 25 months after randomization.

Secondary analyses explored bivariate relationships between mental health symptoms and drug use over time [36]. As mental health symptoms tend to be elevated in HIV-positive individuals compared to the general population, an understanding of the temporal relationship between mood and risk behaviors can better inform the design of behavioral interventions. A particular outcome pair of interest is the Positive State of Mind (PSOM; [38]) and a count of the number of days using drugs other than alcohol or marijuana [36]. The relationship between PSOM and drug use had been explored in cross-sectional studies but not in the longitudinal framework offered by the HLP study; study participants were assessed across six time points. In the study participants randomly assigned to the control arm ($n = 436$), a lower PSOM was associated with increased drug use as indicated by correlations between paired random intercepts ($\hat{\rho} = -0.16$) and paired residuals ($\hat{r} = -0.09$). We conduct power calculations for a hypothetical follow-up study that aims to explore the longitudinal relationship between PSOM and drug use as a primary analysis.

We determine the minimum number of study participants that are needed to test the following pairs of hypotheses: (a) $H_0 : \rho = 0$ against $H_A : \rho = -0.2$; (b) $H_0 : r = 0$ against $H_A : r = -0.2$; (c) $H_0 : \rho_{jj} = 0$ against $H_A : \rho_{jj} = -0.2$; and (d) $H_0 : \rho_{jj'} = 0$ against $H_A : \rho_{jj'} = -0.1$. When calculating power to test $H_0 : \rho = 0$, we set $r = -0.2$ and vice versa. Alternative hypothesis values for ρ_{jj} and $\rho_{jj'}$ are calculated from equations (18) and (19), respectively, after setting $\rho = -0.2$, $r = -0.2$, and setting the variance parameter values to those from the HLP study: $\tau_1^2 = 0.4$, $\tau_2^2 = 4.4$, $\sigma_1^2 = 0.5$, and $\sigma_2^2 = 3.9$. Power calculations were programmed in R version 2.4.1 [7] using our proposed methodology, a one-sample two-sided z -test framework using ML or REML Fisher information to calculate the correlation variances. R code for sample size and power calculations is available from the first author upon request.

An alternative approach that an investigator may use to approximate sample size is based on power calculations for the Pearson product-moment correlation coefficient, typically calculated for cross-sectional data; independence is assumed between pairs of observations both between and within subjects. Therefore, if the total number of observations, including the number of subjects and repeated observations, are assumed to be the same for cross-sectional calculations and our proposed calculations, the estimated variance will be the

smallest for the cross-sectional calculations; power will be overestimated for cross-sectional calculations. By performing cross-sectional calculations for differing numbers of total observations, an investigator can provide power bounds for the true power.

Cross-sectional power calculations are carried out in PASS [15, Chapter 29] by approximating distributions of the Pearson correlation coefficient under the null and alternative hypotheses [39]. Similar power curves are achieved by assuming a normal distribution for the Pearson correlation coefficient, i.e. a z -test framework, and using equation (17) to approximate the correlation variance under the null hypothesis, e.g. the asymptotic variance is $1/n$ under a zero null hypothesis. Even for a small sample size of $n = 10$, the powers are close in value between PASS (power=0.08) and a z -test framework (power=0.09). For $n = 50$, the powers are the same as two digits, i.e. power = 0.29 using both PASS and a z -test framework.

Figure 3 compares cross-sectional power calculations to calculations using ML variances under a longitudinal study design for various sample sizes. Cross-sectional calculations for n and nJ subjects provide lower and upper power bounds, respectively, for the true power on the correlation of the paired residuals. Both lower and upper power bounds are far from the true power for smaller sample sizes. For $n = 50$, Figure 3 shows powers of 0.29, 0.89, and 0.94 for cross-sectional correlation on n subjects, the correlation between residuals, and cross-sectional correlation on nJ subjects. A calculation for correlations on the residuals that assumes a cross-sectional study design can be perfectly mitigated by substituting $J - 1$ for J in that calculation.

While cross-sectional calculations on nJ subjects provide an upper bound for the correlation between paired random intercepts, calculations on n subjects do not provide a lower bound. Correlations on n paired random intercepts are influenced by J repeated measurements that contribute additional variability relative to the cross-sectional correlations on n observations. Figure 3 shows that the power for testing the correlation between paired random intercepts is low in absolute terms. One would need a sample size of more than 250 subjects to get to a power of 0.8. In contrast, the power for the residual correlation is nearly 1 for $n = 100$ subjects with $J = 6$ repeated measurements.

In Figure 3, the power for the marginal concurrent correlation between bivariate observations is lower than the power for the correlation between paired residuals, although hypotheses for both correlations are the same, i.e. the null correlation is zero and the alternative correlation is -0.2 . This difference in power demonstrates the advantage of a model versus non-model-based approach when the model-based approach is appropriate.

Figure 4 compares cross-sectional sample size calculations to our proposed calculations using ML variances under a longitudinal study design. We assume an alpha level of 0.05, 80 per cent power, and zero correlation under the null hypotheses, $H_0 : \rho = 0$, $H_0 : r = 0$, $H_0 : \varrho_{jj} = 0$, and $H_0 : \varrho_{jj'} = 0$. Sample sizes are shown for alternative hypothesis correlations ranging from -0.05 to -0.5 . Figure 4 shows that the difference in sample sizes between correlations for residuals, cross-sectional correlations, and random intercept correlations is quite large for small correlations, e.g. 157, 782, and 1093, respectively, for an alternative hypothesis correlation of -0.1 . The cross-sectional calculations do not provide a suitable upper bound for the required sample size on correlations for random intercepts.

Power and sample size calculations are impacted minimally whether ML or REML correlation variance estimates are used in the formulas. Recall that under REML compared to ML, variance estimates may be slightly smaller or identical, that is variance estimates for $\hat{r}$ when both ρ and r are zero. Even for a small sample size, e.g. $n = 10$, we found REML and ML power estimates in our empirical studies to differ by less than 1 per cent. Likewise, an

investigator would be unlikely to change a proposed sample size based on ML or REML variance estimates.

6. Discussion

We proposed power and sample size calculations for bivariate longitudinal studies where the correlation of the residuals and random intercepts between paired outcomes is of interest. An alternative approach would be to form bounds around the true power using power calculation formulas for the Pearson correlation on cross-sectional observations. While this approach provides power bounds for the correlation of the residuals, the bounds are far from the true power for the correlation of the residuals in smaller samples. The cross-sectional calculations do not provide a lower bound for the correlation of the random intercepts.

Similar to univariate longitudinal studies, data collection must be considered when comparing bivariate longitudinal and cross-sectional designs. Repeatedly assessing characteristics at each time point that could be assessed once in a repeated observations study design, e.g. demographics, reduces other information that can be collected [40, p. 140]. A greater number of correlations can be studied in a repeated measures design. It also may be cheaper to collect data on the same individual over time than to recruit new subjects at each time point [4, Chapter 6].

Power calculations are slightly more conservative under ML compared to REML, though differences would be unlikely to greatly impact the proposed sample size for a study. Under ML, power for the correlation of the residuals reduces to a simple formula and only depends on the number of subjects, number of repeated measurements, and residual correlation; under REML, covariance parameters other than the correlation of the paired residuals also influences the power, though only to a modest extent. Power for the correlation of the random intercepts does not reduce to a simple formula under ML or REML. However, the calculations are easily carried out.

One of the challenges in the design of the bivariate longitudinal study is the selection of appropriate hypothesized values of correlation parameters. Previous bivariate longitudinal analyses from longitudinal study designs are few relative to univariate longitudinal study analyses. If no data are available to determine appropriate values, Cohen's [41, Chapter 3] rules of thumb can be used. He considered correlations of 0.10, 0.30, and 0.50 to be small, medium, and large, respectively. A conservative approach is to choose the correlations smallest in absolute value that you would expect to find for the alternative hypothesized values. As the correlation coefficient increases in absolute value, its variance decreases; therefore, power increases with increasing correlations in absolute value. The random intercept correlation power also depends on the other covariance parameters that need to be considered in the calculations. For example, power on the random intercept correlation increases with increasing random intercept and residual positive correlation and random intercept variance parameter values; power decreases with increasing residual variance parameter values.

Another challenge in the design of the bivariate longitudinal study is the choice of an appropriate covariance structure to represent variability in the phenomenon under study. We assume a bivariate longitudinal model with random intercepts and compound symmetry covariance which is appropriate when a constant relationship between outcomes over time is assumed. If the relationship between outcomes changes over time, e.g. in a random intercept and slope (RIAS) model, then our proposed calculations are not appropriate. Different design questions and different analysis questions are posed than those addressed by our bivariate random intercept power calculations. For example, in a RIAS model, the locations

in time where observations are taken affect the power, and not just the number of observations. In the RIAS model, the random intercepts represent shifts in the mean response levels of subjects from the overall mean at the zero time point, and not across all time points as the random intercept model assumes. RIAS-based research questions usually focus on the correlation between random slopes, and cross-correlations between slopes and the intercepts of the other outcome, and not the correlations between random intercepts. A RIAS analysis that is based on our power calculations will be underpowered. Using our proposed methodology, we conducted a study of power in the example in Section 5 for a model with random intercepts and random slopes, assumed to be independent of the random intercepts and each other. There was a decrease in power for both the correlation of the random intercepts and residuals compared to the proposed power calculations we carried out in Section 5.

More complex correlation structures demand methods for handling a greater number of missing data patterns. Missing data patterns for a bivariate random-intercept model only depend on the number of repeated observations. The temporal relationships between repeated observations, e.g. intermittent missingness versus drop out, also influence power calculations for more complex correlation structures. Subjects who show up late or early for a scheduled appointment affect power calculations; the effects could be to decrease or increase the needed size. Another approach for handling missing data is to consider that a sample size specification is actually a specification of a distribution $g(N)$ on N . Say we want the sample size to be m , meaning that the median of $g(N)$ should be m . As power is usually monotone in N , setting $g(N)$ to have median m implies that the median power of the study design is the power associated with sample size m .

Appendix A

The following sample SAS code can be used to fit a bivariate random intercept model to a pair of continuous outcomes using the PROC MIXED procedure. Further details and examples may be found in [4, Chapter 13] and at Robert Weiss' webpage (http://rem.ph.ucla.edu/rob/rm/new/index.html#Computer_Labs, see lab 8 in particular).

We begin with a SAS data set, TEMP (sketched in outline form in Table A1), that contains observations on n subjects with three repeated measurements each. Each row contains observations on one of two continuous outcomes, y_{ij1} or y_{ij2} , and a continuous time-constant explanatory variable X .

Table A1

Data structure for SAS data set TEMP.

Subject	Response	Indicator	X	Time
1	y_{111}	1	x_1	1
1	y_{112}	2	x_1	1
1	y_{121}	1	x_1	2
1	y_{122}	2	x_1	2
1	y_{131}	1	x_1	3
1	y_{132}	2	x_1	3
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n	y_{n11}	1	x_n	1
n	y_{n12}	2	x_n	1

Subject	Response	Indicator	X	Time
n	y_{n21}	1	x_n	2
n	y_{n22}	2	x_n	2
n	y_{n31}	1	x_n	3
n	y_{n32}	2	x_n	3

Next we fit a bivariate random intercept model with correlated random intercepts (as indicated by the 'RANDOM' statement) and correlated residuals (as indicated by the 'REPEATED' statement) using the following SAS code.

```
PROC MIXED DATA=TEMP2;
  CLASS SUBJECT TIME INDICATOR;
  MODEL RESPONSE=INDICATOR X TIME INDICATOR*X INDICATOR*TIME/ NOINT S;
  RANDOM INDICATOR / TYPE=UN SUBJ=SUBJECT G GCORR;
  REPEATED / TYPE=UN SUBJ=TIME(SUBJECT) R RCORR;
RUN;
```

Appendix B

Specification of the inverse covariance matrix V^{-1}

We note that $(A \otimes B)^{-1} = A^{-1} \otimes B^{-1}$ [42, p. 338] and define $\Omega = \Sigma^{-1}$. The inverses of Σ and T are

$$\Sigma^{-1} = \frac{1}{\sigma_1^2 \sigma_2^2 (1 - r^2)} \begin{pmatrix} \sigma_2^2 & -r\sigma_1\sigma_2 \\ -r\sigma_1\sigma_2 & \sigma_1^2 \end{pmatrix} \quad (\text{B1})$$

and

$$T^{-1} = \frac{1}{\tau_1^2 \tau_2^2 (1 - \rho^2)} \begin{pmatrix} \tau_2^2 & -\rho\tau_1\tau_2 \\ -\rho\tau_1\tau_2 & \tau_1^2 \end{pmatrix}. \quad (\text{B2})$$

The inverse of covariance matrix V [42, p. 426] is

$$V^{-1} = (\Sigma \otimes I_J + ZTZ')^{-1} \quad (\text{B3})$$

$$= \Omega \otimes I_J - (\Omega \otimes I_J)Z(T^{-1} + Z'(\Omega \otimes I_J)Z)^{-1}Z'(\Omega \otimes I_J). \quad (\text{B4})$$

Now because Z is expressed as (4) under a bivariate random intercept model,

$$Z'(\Omega \otimes I_J)Z = (I_2 \otimes \mathbf{1}')(\Omega \otimes I_J)(I_2 \otimes \mathbf{1}) \quad (\text{B5})$$

$$=(I_2 \Omega \otimes \mathbf{1}' I_j)(I_2 \otimes \mathbf{1}) \quad (\text{B6})$$

$$=J\Omega. \quad (\text{B7})$$

Finally

$$V^{-1}=\Omega \otimes I_j - (\Omega \otimes I_j)Z(T^{-1}+J\Omega)^{-1}Z'(\Omega \otimes I_j). \quad (\text{B8})$$

Appendix C

Specification of the inverse of $X'V^{-1}X$

We consider an intercept only model where the covariate matrix and random effect covariate matrix are equivalent, $X = Z = (I_2 \otimes \mathbf{1}_j)$. Then $X'V^{-1}X$ is

$$X'V^{-1}X=(I_2 \otimes \mathbf{1}')(\Omega \otimes I_j - (\Omega \otimes I_j)Z(T^{-1}+J\Omega)^{-1}Z'(\Omega \otimes I_j))(I_2 \otimes \mathbf{1}) \quad (\text{C1})$$

$$=J\Omega - J\Omega(T^{-1}+J\Omega)^{-1}J\Omega. \quad (\text{C2})$$

Finally

$$(X'V^{-1}X)^{-1}=(J\Omega)^{-1}-(J\Omega)^{-1}(-J\Omega)(T^{-1}+J\Omega+(J\Omega)(J\Omega)^{-1}(-J\Omega))^{-1}(J\Omega)(J\Omega)^{-1} \quad (\text{C3})$$

$$=\frac{\Sigma}{J}+T. \quad (\text{C4})$$

Appendix D

Specification of the second derivative of $\sum_{i=1}^n \log |X_i'V^{-1}X_i|$

For brevity of notation we set $\sum_{i=1}^n \log |X_i'V^{-1}X_i|=n \log |X'V^{-1}X|$, though results apply to the general case where each subject has its own design matrix, X_i . The second derivative of $\log |X'V^{-1}X|$ [42, p. 309] is

$$\frac{\partial^2 \log |X'V^{-1}X|}{\partial \theta_r \partial \theta'_s} = \text{tr} \left((X'V^{-1}X)^{-1} \frac{\partial^2 (V^{-1}X)}{\partial \theta_r \partial \theta'_s} \right) \quad (\text{D1})$$

$$\begin{aligned}
& -\text{tr} \left((X'V^{-1}X)^{-1} \frac{X'\partial(V^{-1})X}{\partial\theta_r} (X'V^{-1}X)^{-1} \frac{X'\partial(V^{-1})X}{\partial\theta_s} \right) \\
& = \text{tr} \left((X'V^{-1}X)^{-1} X' \left(V^{-1} \frac{\partial(V)}{\partial\theta_r} V^{-1} \frac{\partial(V)}{\partial\theta_s} V^{-1} \right. \right. \\
& \quad \left. \left. + V^{-1} \frac{\partial(V)}{\partial\theta_s} V^{-1} \frac{\partial(V)}{\partial\theta_r} V^{-1} \right. \right. \\
& \quad \left. \left. - V^{-1} \frac{\partial^2 V}{\partial\theta_r \partial\theta_s} V^{-1} \right. \right. \\
& \quad \left. \left. - V^{-1} \frac{\partial(V)}{\partial\theta_r} V^{-1} X (X'V^{-1}X)^{-1} X' V^{-1} \frac{\partial(V)}{\partial\theta_s} V^{-1} X \right. \right.
\end{aligned} \tag{D2}$$

Appendix E

We provide the expression for the derivative matrix $D = \partial(\varrho_{jj'})/\partial(\theta)$ in Section 3.1 for $j = j'$ and $j \neq j'$. Recall that $\theta = (\tau_1, \tau_2, \rho, \sigma_1, \sigma_2, r)'$. Let $\eta = \tau_{12} + \sigma_{12} = \rho\tau_1\tau_2 + r\sigma_1\sigma_2$ and

$\omega = \sqrt{(\tau_1^2 + \sigma_1^2)(\tau_2^2 + \sigma_2^2)}$. For the correlation between concurrent time points,

$\varrho_{jj} = (\tau_{12} + \sigma_{12}) / \sqrt{(\tau_1^2 + \sigma_1^2)(\tau_2^2 + \sigma_2^2)}$, the elements of D are

$$\begin{aligned}
\frac{\partial(\varrho_{jj})}{\partial(\tau_1)} &= \frac{\rho\tau_2}{\omega} - \frac{\tau_1\eta(\tau_2^2 + \sigma_2^2)}{\omega^3}, & \frac{\partial(\varrho_{jj})}{\partial(\tau_2)} &= \frac{\rho\tau_1}{\omega} - \frac{\tau_2\eta(\tau_1^2 + \sigma_1^2)}{\omega^3}, & \frac{\partial(\varrho_{jj})}{\partial(\rho)} &= \frac{\tau_1\tau_2}{\omega}, \\
\frac{\partial(\varrho_{jj})}{\partial(\sigma_1)} &= \frac{r\sigma_2}{\omega} - \frac{\sigma_1\eta(\tau_2^2 + \sigma_2^2)}{\omega^3}, & \frac{\partial(\varrho_{jj})}{\partial(\sigma_2)} &= \frac{r\sigma_1}{\omega} - \frac{\sigma_2\eta(\tau_1^2 + \sigma_1^2)}{\omega^3}, & \frac{\partial(\varrho_{jj})}{\partial(r)} &= \frac{\sigma_1\sigma_2}{\omega}.
\end{aligned}$$

For the correlation between lagged time points, $\varrho_{jj'} = \tau_{12} / \sqrt{(\sigma_1^2 + \tau_1^2)(\sigma_2^2 + \tau_2^2)}$, the elements of D are

$$\begin{aligned}
\frac{\partial(\varrho_{jj'})}{\partial(\tau_1)} &= \frac{\rho\tau_2}{\omega} - \frac{\rho\tau_1\tau_2(\tau_2^2 + \sigma_2^2)}{\omega^3}, & \frac{\partial(\varrho_{jj'})}{\partial(\tau_2)} &= \frac{\rho\tau_1}{\omega} - \frac{\rho\tau_1\tau_2(\tau_1^2 + \sigma_1^2)}{\omega^3}, & \frac{\partial(\varrho_{jj'})}{\partial(\rho)} &= \frac{\tau_1\tau_2}{\omega}, \\
\frac{\partial(\varrho_{jj'})}{\partial(\sigma_1)} &= -\frac{\rho\tau_1\tau_2\sigma_1(\tau_2^2 + \sigma_2^2)}{\omega^3}, & \frac{\partial(\varrho_{jj'})}{\partial(\sigma_2)} &= -\frac{\rho\tau_1\tau_2\sigma_2(\tau_1^2 + \sigma_1^2)}{\omega^3}, & \frac{\partial(\varrho_{jj'})}{\partial(r)} &= 0.
\end{aligned}$$

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Figure 1.

Comparison of ML variances for correlations between random intercepts, $\text{Var}(\hat{\rho})$, estimated from simulation studies on the x-axis and calculated from asymptotic formulas on the y-axis. Data point clusters (3 points each) represent variances for $\rho = 0.2$ (●), 0.5 (△), and 0.8 (▽), respectively. The dashed line represents equation for $y = x$.

Figure 2.

Comparison of ML variances for correlations between residuals, $\text{Var}(\hat{r})$, estimated from simulation studies on the x -axis and calculated from asymptotic formulas on the y -axis. Starting from lower left corner to upper right corner, data point clusters (3 points each) represent variances for $r = 0.8, 0.5$, and 0.2 , respectively. Within each cluster, values of ρ are $\bullet = 0.2$, $\triangle = 0.5$, and $\nabla = 0.8$. The dashed line represents equation for $y = x$.

Figure 3.

Power calculations for correlations between paired random intercepts, residuals, and bivariate observations on n subjects each with $J = 6$ repeated observations. Cross-sectional power calculations for correlations on n and $4n$ subjects are shown for reference. Correlation values under the zero null hypothesis are $\rho = 0$ and $r = 0$ and correlation values under the alternative hypothesis are $\rho = -0.2$ and $r = -0.2$. Variance parameter values are $\tau_1^2 = 0.4$, $\tau_2^2 = 4.4$, $\sigma_1^2 = 0.5$, and $\sigma_2^2 = 3.9$. Power calculations for the correlation between paired random intercepts and lagged bivariate observations result in identical power curves under the zero null hypothesis.

Figure 4.

Sample size calculations for correlations between paired random intercepts, residuals, and bivariate observations for 80 per cent power and $J = 6$ repeated observations. Cross-sectional and compound symmetry sample size calculations are shown for reference. Correlation values under the zero null hypothesis are $\rho = 0$ and $r = 0$. Variance parameter values are $\tau_1^2=0.4$, $\tau_2^2=4.4$, $\sigma_1^2=0.5$, and $\sigma_2^2=3.9$. Sample size calculations for the correlation between paired random intercepts and lagged bivariate observations result in identical sample size curves under the zero null hypothesis.

Table I

The variance of $\hat{\rho}$ for differing values of covariance parameters for $n = 50$, $J = 4$, and for $r = 0.5$ except for the first three rows where $^a r = 0.2$, $^b r = 0.5$, and $^c r = 0.8$.

Ratio	ML Var($\hat{\rho}$)			REML Var($\hat{\rho}$)		
	τ_1^2/σ_1^2	τ_2^2/σ_2^2	ρ	ρ	ρ	ρ
1	1 ^a		0.02918	0.01950	0.00739	0.02858
1	1 ^b		0.02857	0.01781	0.00550	0.02794
1	1 ^c		0.02827	0.01650	0.00410	0.02759
0.25	1		0.04615	0.03021	0.01385	0.04505
0.5	1		0.03443	0.02173	0.00767	0.03364
2	1		0.02569	0.01602	0.00470	0.02513
4	1		0.02430	0.01525	0.00444	0.02378
0.25	0.25		0.07699	0.04875	0.02323	0.07481
0.5	0.5		0.04171	0.02625	0.00991	0.04071
2	2		0.02313	0.01430	0.00386	0.02263
4	4		0.02069	0.01271	0.00318	0.02025

Table II

Conclusions from empirical results for effect of covariance parameters on correlation variances $\text{Var}(\hat{\rho})$ and $\text{Var}(\hat{r})$

Covariance parameter	ML/REML $\text{Var}(\hat{\rho})$	ML $\text{Var}(\hat{r})$	REML $\text{Var}(\hat{r})$
Increasing ρ from 0 to 1 in absolute value	↓		
Increasing ρ from -1 to 1		↔	↓
Increasing r from 0 to 1 in absolute value		↓	↓
Increasing r from -1 to 1	↓		
Increasing τ_1^2 and or τ_2^2	↓	↔	↑
Increasing σ_1^2 and or σ_2^2	↑	↔	↓
Multiplying τ_1^2 and σ_1^2 or τ_2^2 and σ_2^2 by single constant	↔	↔	↔

↓ Decreases; ↑ Increases; ↔ No change.

Square roots of mean squared errors (RMSE), standard deviation estimates (SD), and biases of correlation parameters from ML simulation studies on data sets of size 250 and 4 repeated measurements.

Table III

<i>r</i>	RMSE($\hat{r}$)	SD($\hat{r}$)	Bias($\hat{r}$)	ρ	RMSE($\hat{\rho}$)	SD($\hat{\rho}$)	Bias($\hat{\rho}$)
0.2	0.0394	0.0394	0.0003	0.2	0.0646	0.0646	-0.0004
0.2	0.0346	0.0345	0.0027	0.5	0.0646	0.0646	-0.0011
0.2	0.0383	0.0379	0.0055	0.8	0.0322	0.0322	0.0008
0.5	0.0262	0.0261	0.0014	0.2	0.0692	0.0672	0.0162
0.5	0.0293	0.0292	0.0006	0.5	0.0551	0.0549	0.0038
0.5	0.0265	0.0263	0.0029	0.8	0.0345	0.0344	0.0026
0.8	0.0118	0.0118	0.0003	0.2	0.0699	0.0698	0.0042
0.8	0.0143	0.0142	-0.0011	0.5	0.0497	0.0493	-0.0061
0.8	0.0110	0.0109	0.0007	0.8	0.0274	0.0270	0.0049

Comparison of variances for correlation ρ between random intercepts and correlation r between residuals, estimated from ML simulation studies and ML asymptotic formulas, for four unbalanced data sets and three balanced data sets ($n = 250$).

Table IV

Number of subjects with J obs where			Simulation study variance		Asymptotic variance	
$J = 2$	$J = 4$	$J = 6$	ρ	r	ρ	r
125	125		0.0039	0.0018	0.0073	0.0016
	125	125	0.0056	0.0008	0.0051	0.0009
125		125	0.0061	0.0009	0.0059	0.0012
75	75	100	0.0047	0.0011	0.0056	0.0011
250			0.0079	0.0025	0.0080	0.0037
	250		0.0042	0.0015	0.0054	0.0012
			0.0034	0.0007	0.0048	0.0007

Variance parameter values are $\tau_1^2=1, \tau_2^2=3, \sigma_1^2=1, \sigma_2^2=2, \rho=0.2$ and $r=0.2$.