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A Bivariate Mixed-Effects Location-Scale Model with application to Ecological Momentary Assessment (EMA) data

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Abstract

A bivariate mixed-effects location-scale model is proposed for estimation of means, variances, and covariances of two continuous outcomes measured concurrently in time and repeatedly over subjects. Modeling the two outcomes jointly allows examination of BS and WS association between the outcomes and whether the associations are related to covariates. The variance-covariance matrices of the BS and WS effects are modeled in terms of covariates, explaining BS and WS heterogeneity. The proposed model relaxes assumptions on the homogeneity of the within-subject (WS) and between-subject (BS) variances. Furthermore, the WS variance models are extended by including random scale effects. Data from a natural history study on adolescent smoking are used for illustration. 461 students, from 9th and 10th grades, reported on their mood at random prompts during seven consecutive days. This resulted in 14,105 prompts with an average of 30 responses per student. The two outcomes considered were a subject's positive affect and a measure of how tired and bored they were feeling. Results showed that the WS association of the outcomes was negative and significantly associated with several covariates. The BS and WS variances were heterogeneous for both outcomes, and the variance of the random scale effects were significantly different from zero.

Keywords

Covariance modeling; Variance modeling; Bivariate model; EMA data; Random scale; Clustered data

1. Introduction

An important aspect of modern data collection in health science pertains to concurrent measurement of several outcomes on the same subject. Often, these multiple outcomes are measured repeatedly which produce observations clustered within subjects. The current practice in many areas is usually to model these outcomes separately and draw conclusions

based on the separate models. However, the separate models do not take into account the relationship between the outcomes. Thus, it is more efficient and informative to model the concurrent outcomes simultaneously. Recent applications of bivariate repeated measurement data analysis include the natural history of disease (Inoue et al. 2008), self-rated health and functional status (Hubbard et al. 2009), human sexual behavior (Ghosh and Tu 2008), and drug prescribing habits in general practice (Sithole and Jones 2007).

When treating outcomes separately, mixed-effects models (Laird and Ware 1982) are a popular method for analyzing repeated measurements data. These models often include one or more random effects and allow separate estimation of the between- (BS) and within-subject (WS) variances. The BS and WS variances are usually treated as being homogeneous across subjects. Typically, the random effects are taken to be normally distributed, which assumes a unimodal distribution of change of the outcome for all participants. However, in situations with heterogeneous populations this assumption may not be correct and can lead to poor estimates of the covariance matrix (Verbeke and Lesaffre 1997) or can obscure important features of the BS variation (Zhang and Davidian 2001). In addition, focusing on mean estimation and treating variance as a nuisance parameter might lead to inefficient estimation and misleading conclusions (Carroll 2003).

There are several approaches that investigators have developed to take into account heterogeneous populations under study. Elliott (2007) developed methods for estimating latent clusters of variability that can be related to subject-level predictors. Balazs, Hidegkuti, and De Boeck (2006) examined participant heterogeneity in item-response data via a logistic regression model in which heterogeneity appeared as a latent random effect added to the main effects and covariate dependent terms. Pourahmadi (2000) developed a modified Cholesky decomposition to model the marginal covariance matrix in terms of covariates. Daniels and Zhao (2003) studied generalized linear mixed models in the context of clustered data allowing the covariance matrix of the random effects to differ from subject to subject. Pourahmadi and Daniels (2002) proposed dynamic conditionally-linear mixed models, that allowed flexibility in modeling the variance-covariance structure in terms of covariates with random effects. Hedeker et al. (2006) and Hedeker and Mermelstein (2007) have described mixed-effects model approaches incorporating modeling of the WS variance.

In addition to specifying a random component for the mean of the response, models can be extended by including a random effect for the WS variance. Hedeker et al. (2008) described this approach, with application to ecological momentary assessment (EMA) data, in a study that focused on characterizing changes in mood variation. EMA and/or real-time data captures have been developed to record the momentary events and experiences of subjects in daily life (Bolger et al. 2003), and such procedures yield relatively large numbers of observations per subject. By including a subject-level random effect to the WS variance specification, the model allows subjects to have influence on both the mean, or location, and on the variability, or square of the scale, of their mood responses. Such mixed-effects location-scale models have useful applications where interest centers on the joint modeling of the mean and variance structure.

In this paper, the model proposed by Hedeker et al. (2008) is extended to allow the modeling of two outcomes jointly with a bivariate mixed-effects location-scale model. An important innovation of the proposed model is that it separates the covariance of two outcomes into WS and BS components, and allows examination of how these two covariance components differ between subgroups of subjects. Specifically, we consider the joint modeling of two outcomes measured simultaneously and repeatedly, using EMA, on the same subjects. The outcomes represent continuous measurements of mood. Specifying a joint bivariate normal distribution for the random intercepts (of the mean models) allows taking into account any correlation between the mood measurements at the subject level. In addition to these correlated random location effects, the error terms are assumed to follow a bivariate normal distribution, and the error covariance is modeled to allow WS dependence of the two outcomes. The extension over existing models for bivariate normal clustered outcomes is that elements of the variance-covariance matrices of both the error terms and of the random intercepts are modeled in terms of covariates, allowing for and explaining BS and WS heterogeneity. The WS variance models of both outcomes are further extended by including random effects to allow for subject variability in variance that is not explained by covariates (i.e., random scale effects). The two correlated random location and two correlated random scale effects are jointly modeled in terms of a multivariate normal distribution with an unstructured variance-covariance matrix.

The remainder of this article is organized as follows. In Section 2, we specify the bivariate mixed-effects location-scale model with heterogeneous BS and WS variances. Estimation of the proposed model is described in Section 3 and calculations for BS and WS correlation and ICC are presented in Section 4. In Sections 5, the empirical performance of the proposed model is studied by simulations and its real-life application is illustrated by modeling two mood measures from the adolescent EMA study. We conclude with brief remarks in Section 6.

2. Bivariate Mixed-Effects Location-Scale Model

Let us define a general bivariate linear mixed-effects model which includes a random

intercept and error. Consider $\mathbf{Y}_i = \begin{bmatrix} \mathbf{Y}_i^{(1)} \\ \mathbf{Y}_i^{(2)} \end{bmatrix}$ as the response vector for the subject i ($i = 1, 2, \dots, N$), where $\mathbf{Y}_i^{(k)}$ is the $n_i^{(k)}$ -vector of measurements of the outcome k ($k = 1, 2$) with $n_i^{(1)} = n_i^{(2)} = n_i$. Occasions of measurement are indexed by j ($j = 1, 2, \dots, n_i$). Superscripts in all formula notations represent the two outcomes and are enclosed in parenthesis to distinguish from other notation.

To take into account the association between outcomes we can specify the following bivariate linear mixed model:

$$\mathbf{Y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{u}_i + \boldsymbol{\varepsilon}_i \quad (1)$$

with

$$\begin{cases} \varepsilon_i \sim N(\mathbf{0}, \Sigma_i) \\ \mathbf{u}_i \sim N(\mathbf{0}, G) \end{cases} \quad (2)$$

where $\mathbf{X}_i = \begin{bmatrix} \mathbf{X}_i^{(1)} & \mathbf{0} \\ \mathbf{0} & \mathbf{X}_i^{(2)} \end{bmatrix}$ is a $2n_i \times (p^{(1)} + p^{(2)})$ design matrix of fixed effects, $\boldsymbol{\beta} = \begin{bmatrix} \boldsymbol{\beta}^{(1)} \\ \boldsymbol{\beta}^{(2)} \end{bmatrix}$ is a $p^{(1)} + p^{(2)}$ -vector of fixed effect parameters, $\mathbf{Z}_i = \begin{bmatrix} \mathbf{1}_{n_i} & \mathbf{0} \\ \mathbf{0} & \mathbf{1}_{n_i} \end{bmatrix}$ is a $2n_i \times 2$ matrix of 0 and 1, $\mathbf{u}_i = \begin{bmatrix} u_i^{(1)} \\ u_i^{(2)} \end{bmatrix}$ is a vector of an individual's random effects and $\boldsymbol{\varepsilon}_i = \begin{bmatrix} \varepsilon_i^{(1)} \\ \varepsilon_i^{(2)} \end{bmatrix}$ represents independent measurement errors.

The covariance matrix of the random effects is the matrix $G = \begin{bmatrix} \sigma_{u^{(1)}}^2 & \sigma_{u^{(1)}u^{(2)}} \\ \sigma_{u^{(1)}u^{(2)}} & \sigma_{u^{(2)}}^2 \end{bmatrix}$. The covariance matrix of measurement errors is defined by $\Sigma_i = \Sigma \otimes \mathbf{I}_{n_i}$, where

$\Sigma = \begin{bmatrix} \sigma_{\varepsilon^{(1)}}^2 & \sigma_{\varepsilon^{(1)}\varepsilon^{(2)}} \\ \sigma_{\varepsilon^{(1)}\varepsilon^{(2)}} & \sigma_{\varepsilon^{(2)}}^2 \end{bmatrix}$ (the symbol $\otimes$ represents the Kronecker product). Note that Σ_i is dependent on i through its dimension n_i , however the set of parameters for Σ_i is not dependent on i in this model formulation. The random effects as well as the error terms are correlated in this model specification, which induces correlation between the two responses.

We can further extend the model by allowing for participant's heterogeneity via modeling of the BS and WS variance and covariance, and by including random subject effects for a subject's measurement error (i.e., random scale effects). For this, the variance-covariance matrix of the random effects and random errors are modeled by means of covariates using a log link function, which has been described in the context of heteroskedastic fixed-effects regression models (Harvey 1976; Aitkin 1987).

The model can now be written as:

$$\mathbf{Y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{u}_i + \boldsymbol{\varepsilon}_i \quad (3)$$

$$\log(\sigma_{u_i^{(k)}}^2) = (\mathbf{V}_i^{(k)})^T \boldsymbol{\tau}^{(k)} \quad (4)$$

$$\sigma_{u_i^{(1)}u_i^{(2)}} = (\mathbf{V}_i^{(12)})^T \boldsymbol{\tau}^{(12)} \quad (5)$$

$$\log(\sigma_{\varepsilon_{ij}^{(k)}}^2) = (\mathbf{W}_{ij}^{(k)})^T \boldsymbol{\gamma}^{(k)} + \omega_i^{(k)} \quad (6)$$

$$\sigma_{\varepsilon_{ij}^{(1)} \varepsilon_{ij}^{(2)}} = \left(\mathbf{W}_{ij}^{(12)} \right)^T \boldsymbol{\gamma}^{(12)} \quad (7)$$

with

$$\begin{bmatrix} \mathbf{u}_i \\ \boldsymbol{\omega}_i \end{bmatrix} \sim N(\mathbf{0}, \mathbf{G}_i)$$

and

$$\boldsymbol{\varepsilon}_i | \mathbf{u}_i, \boldsymbol{\omega}_i = \begin{bmatrix} \varepsilon_{i1}^{(1)} | \mathbf{u}_i^{(1)}, \boldsymbol{\omega}_i^{(1)} \\ \varepsilon_{i2}^{(1)} | \mathbf{u}_i^{(1)}, \boldsymbol{\omega}_i^{(1)} \\ \vdots \\ \varepsilon_{in_i}^{(1)} | \mathbf{u}_i^{(1)}, \boldsymbol{\omega}_i^{(1)} \\ \varepsilon_{i1}^{(2)} | \mathbf{u}_i^{(2)}, \boldsymbol{\omega}_i^{(2)} \\ \vdots \\ \varepsilon_{in_i}^{(2)} | \mathbf{u}_i^{(2)}, \boldsymbol{\omega}_i^{(2)} \end{bmatrix} \sim N(\mathbf{0}, \Sigma_i(\boldsymbol{\omega}_i)) \quad (8)$$

where the meaning and structure of $\mathbf{Y}_i$, $\mathbf{X}_i$, $\boldsymbol{\beta}$, and $\mathbf{Z}_i$ matrices in equation (3) are the same as described earlier. Also, $\mathbf{V}_i^{(k)}$ is a $s^{(k)}$ -vector of covariates for the BS variance, $\mathbf{V}_i^{(12)}$ is a $s^{(12)}$ -vector of covariates for the BS covariance, $\mathbf{W}_{ij}^{(k)}$ is a $d^{(k)}$ -vector of covariates for the WS variance, and $\mathbf{W}_{ij}^{(12)}$ is a $d^{(12)}$ -vector of covariates for the WS covariance, $k = 1, 2$. The set of covariates and corresponding parameters can differ among equations (3)–(7). The set of covariates can also differ by the modeled outcome (k index). The number of parameters associated with these variances and covariances do not vary with subjects or measurements. All vectors of covariates include one as a first element for the BS or WS reference variances and BS and WS reference covariances.

Equation (8) specifies a conditional distribution for the error vector $\boldsymbol{\varepsilon}_i$ given the vector of random location and scale effects $(\mathbf{u}_i^T, \boldsymbol{\omega}_i^T)^T$. The variance-covariance matrix Σ_i of the error vector $\boldsymbol{\varepsilon}_i$ has dimension $2n_i \times 2n_i$ and the following structure:

$$\Sigma_i(\boldsymbol{\omega}_i) = \begin{bmatrix} \sigma_{\varepsilon_{i1}^{(1)}}^2 & 0 & \sigma_{\varepsilon_{i1}^{(1)} \varepsilon_{i1}^{(2)}} & 0 \\ & \ddots & & \ddots \\ 0 & \sigma_{\varepsilon_{in_i}^{(1)}}^2 & 0 & \sigma_{\varepsilon_{in_i}^{(1)} \varepsilon_{in_i}^{(2)}} \\ \sigma_{\varepsilon_{i1}^{(1)} \varepsilon_{i1}^{(2)}} & 0 & \sigma_{\varepsilon_{i1}^{(2)}}^2 & 0 \\ & \ddots & & \ddots \\ 0 & \sigma_{\varepsilon_{in_i}^{(1)} \varepsilon_{in_i}^{(2)}} & 0 & \sigma_{\varepsilon_{in_i}^{(2)}}^2 \end{bmatrix} \quad (9)$$

Elements on the main diagonal of matrix Σ_i are modeled with equation (6) and nonzero elements off the main diagonal of matrix Σ_i (WS covariance terms) are modeled with equation (7). Note that there is no random subject effect associated with the covariance term $\sigma_{\varepsilon_{ij}^{(1)} \varepsilon_{ij}^{(2)}}$ in this model specification.

The overall variance-covariance matrix for the random effects is

$$\mathbf{G}_i = \begin{bmatrix} \sigma_{u_i^{(1)}}^2 & \sigma_{u_i^{(1)} u_i^{(2)}} & \sigma_{u_i^{(1)} \omega_i^{(1)}} & \sigma_{u_i^{(1)} \omega_i^{(2)}} \\ \sigma_{u_i^{(1)} u_i^{(2)}} & \sigma_{u_i^{(2)}}^2 & \sigma_{u_i^{(2)} \omega_i^{(1)}} & \sigma_{u_i^{(2)} \omega_i^{(2)}} \\ \sigma_{u_i^{(1)} \omega_i^{(1)}} & \sigma_{u_i^{(2)} \omega_i^{(1)}} & \sigma_{\omega_i^{(1)}}^2 & \sigma_{\omega_i^{(1)} \omega_i^{(2)}} \\ \sigma_{u_i^{(1)} \omega_i^{(2)}} & \sigma_{u_i^{(2)} \omega_i^{(2)}} & \sigma_{\omega_i^{(1)} \omega_i^{(2)}} & \sigma_{\omega_i^{(2)}}^2 \end{bmatrix} \quad (10)$$

Modeling the two outcomes jointly permits both the location random effect covariance $\sigma_{u_i^{(1)} u_i^{(2)}}$ and the scale random effect covariance $\sigma_{\omega_i^{(1)} \omega_i^{(2)}}$ to be estimated in the model.

The distribution of the random location effects $\mathbf{u}_i$ and random scale effects $\boldsymbol{\omega}_i$ is a multivariate normal with zero mean and variance-covariance matrix $\mathbf{G}_i$ as defined in equation (10). Elements $G_{i,11}$, and $G_{i,22}$ of matrix $\mathbf{G}_i$ are modeled by equation (4) using a log link function for the random location variances, and elements $G_{i,12} = G_{i,21}$ are modeled by equation (5) using a linear model. Other elements of the variance-covariance matrix $\mathbf{G}_i$ are not modeled and estimated as parameters on their own.

Since the distribution of $\omega_i^{(k)}$ is specified as normal, the WS variances follow a log-normal distribution at the individual level. The skewed, nonnegative nature of the log-normal distribution makes it a reasonable choice for representing variances. It has been used in many diverse research areas for this purpose (Shenk et al. 1998; Fowler and Whitlock 1999; Reno and Rizza 2003).

In this model, $u_i^{(k)}$ is a random effect that influences the location or mean of the individual's outcome k , and $\omega_i^{(k)}$ is a random effect that influences individual's variances or square of the scale of outcome k . Thus, the model is expanded with both types of random effects and can be called a bivariate mixed-effects location-scale model. Covariance between the random location and random scale effects indicate the degree to which the random effects are associated with each other.

Although the mean models are specified with random intercepts only, modeling of the WS and BS variances guarantees more complex structure of the variance and covariance of the data than a simple compound symmetry structure. A compound symmetry structure would ensure only in a situation where models for both the WS and BS variances and covariances do not include any predictors.

3. Estimation

Given the above assumptions, the conditional distribution of the outcomes $\mathbf{Y}_i$ is

$$\mathbf{Y}_i | \mathbf{u}_i, \boldsymbol{\omega}_i \sim N(\mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{u}_i, \boldsymbol{\Sigma}_i(\boldsymbol{\omega}_i)) \quad (11)$$

Given the model formulation, the contribution of a subject to the likelihood is $f(\mathbf{Y}_i | \mathbf{u}_i, \boldsymbol{\omega}_i, \boldsymbol{\theta}) g(\mathbf{u}_i, \boldsymbol{\omega}_i)$, where $\mathbf{Y}_i = (\mathbf{Y}_i^{(1)T}, \mathbf{Y}_i^{(2)T})^T$ is a vector of responses for subject i , $(\mathbf{u}_i^T, \boldsymbol{\omega}_i^T)^T$ is a vector of random location and scale effects, $\boldsymbol{\theta} = (\boldsymbol{\beta}^T, \boldsymbol{\gamma}^T, \boldsymbol{\tau}^T)^T$ is a vector of parameters: fixed effects for the means $\boldsymbol{\beta}$, error term covariance matrix $\boldsymbol{\gamma}$, and the random effect covariance matrix $\boldsymbol{\tau}$. The random effects $(\mathbf{u}_i^T, \boldsymbol{\omega}_i^T)^T$ have a distributional assumption of $N(\mathbf{0}, \mathbf{G}_i)$. Under assumptions that the outcomes follow a bivariate conditional normal distribution and the random effects, both location and scale random effects, follow a multivariate normal distribution, the distribution functions for the outcomes and random effects can be written as the following.

$$f(\mathbf{Y}_i | \mathbf{u}_i, \boldsymbol{\omega}_i) = \frac{1}{(2\pi)^{n_i} |\boldsymbol{\Sigma}_i(\boldsymbol{\omega}_i)|^{0.5}} \exp \left\{ -\frac{1}{2} (\mathbf{Y}_i - \mathbf{X}_i \boldsymbol{\beta} - \mathbf{Z}_i \mathbf{u}_i)^T \boldsymbol{\Sigma}_i^{-1}(\boldsymbol{\omega}_i) (\mathbf{Y}_i - \mathbf{X}_i \boldsymbol{\beta} - \mathbf{Z}_i \mathbf{u}_i) \right\} \quad (12)$$

$$g(\mathbf{u}_i, \boldsymbol{\omega}_i) = \frac{1}{(2\pi)^2 |\mathbf{G}_i|^{0.5}} \exp \left\{ -\frac{1}{2} (\mathbf{u}_i^T, \boldsymbol{\omega}_i^T)^T \mathbf{G}_i^{-1} (\mathbf{u}_i, \boldsymbol{\omega}_i) \right\} \quad (13)$$

The marginal density of $\mathbf{Y}_i$ is then $h(\mathbf{Y}_i) = \int \mathbf{u}, \boldsymbol{\omega} f(\mathbf{Y}_i | \mathbf{u}, \boldsymbol{\omega}) g(\mathbf{u}, \boldsymbol{\omega}) d\mathbf{u} d\boldsymbol{\omega}$. The marginal log

likelihood from N subject can be expressed as $L = \sum_{i=1}^N \log h(\mathbf{Y}_i)$. For the current model, the marginal likelihood does not have a closed form solution. Numerical integration methods, such as Gauss-Hermite quadrature, combined with an iterative solving procedure like Newton-Raphson, can be implemented to obtain the parameter estimates. In particular, SAS PROC NL MIXED can be used for this purpose, and syntax for the analyses presented in this paper is available from the first author upon request.

4. Correlation and ICC for Subgroups of Subjects and/or Measurements

The variance and covariance of $y_{ij}^{(k)}$ has a different form based on the values of i, j , and k .

$$\text{Var}(y_{ij}^{(k)}) = \sigma_{u_i}^2 + \exp \left((W_{ij}^{(k)})^T \boldsymbol{\gamma}^{(k)} + \frac{1}{2} \sigma_{\omega}^2 \right), k=1, 2, \text{cov}(y_{ij}^{(k)}, y_{ij'}^{(k')}) = \begin{cases} \sigma_{u_i}^2 & k=k', j \neq j' \\ \sigma_{u_i}^{(k)} u_i^{(k')} & k \neq k', j \neq j' \\ \sigma_{u_i}^{(k)} u_i^{(k')} + \sigma_{\varepsilon_{ij}^{(k)} \varepsilon_{ij'}^{(k')}} & k \neq k', j = j' \end{cases}$$

Using the formulas above, one can estimate the marginal correlation between the two outcomes.

In some cases, it is of interest to express the BS variability in terms of an intraclass correlation coefficient (ICC). The ICC represents the degree of association of the data within subjects and is calculated as $\sigma_u^2 / (\sigma_u^2 + \sigma_\varepsilon^2)$. Since our model relaxes the assumptions of

variance homogeneity (both BS and WS), we can estimate the ICC for different subgroups of subjects and/or measurements as:

$$ICC_{ij,ij'}(k) = \frac{\sigma_{u_i}^2(k)}{\sqrt{\left(\sigma_{u_i}^2(k) + \exp\left((W_{ij}^{(k)})^T \gamma^{(k)} + \frac{1}{2}\sigma_{\omega}^2(k)\right)\right)\left(\sigma_{u_i}^2(k) + \exp\left((W_{ij'}^{(k)})^T \gamma^{(k)} + \frac{1}{2}\sigma_{\omega}^2(k)\right)\right)}} \quad k=1, 2$$

where indices i and j indicate that the ICC depends on subject i and measurement j . In other words, when the model includes time-varying covariates for the WS component, the ICC value differs not only by subjects but also within a subject across measurements.

5. Simulation Study and Results

A series of simulations were carried out to evaluate the accuracy of the proposed model (3)–(8) and the potential gain in efficiency for joint modeling versus separate modeling of the two outcomes. In order for the simulation results to be generalizable and have credibility, the simulated data were generated to have close similarity to real data (Burton et al. 2006). One thousand datasets were generated with correlated random location and scale effects, plus correlated errors, using gender as a covariate (GenderM: females=0 and males=1); the “true” parameter values are listed in Table 1. These generated datasets were then analyzed using two different model specifications:

- S1. Bivariate mixed-effects model with correlated random location effects and correlated errors, but without random scale effects;
- S2. Bivariate mixed-effects location-scale model with correlated random location and scale effects, plus correlated errors.

Model S1 specifies a bivariate linear mixed-effects model in which dependency between the two outcome variables is induced by non-zero BS and WS correlations for the location random effects and error variance matrices, respectively. Parameters for the BS and WS covariance are estimated in this model. The BS covariance is allowed to vary between genders, and is modeled with gender as a linear predictor. The BS and WS variances are also allowed to vary between genders, and modeled by log-normal models with gender as a covariate. In contrast to the subsequent Model S2, Model S1 does not allow for random subject scale effects.

Model S2, by adding random scale effects, is the model that underlies the simulated data. This model assumes that the two outcomes are correlated and models the dependency of the outcomes via correlated random effects and correlated error terms. The BS and WS variances are allowed to vary between and within subjects, respectively, and modeled by log-normal models with gender as a covariate. In addition, each WS variance model includes a random subject scale parameter, which characterizes the variability in the WS variance that is not explained by the covariates.

For each simulated dataset, a set of estimated parameters and their standard errors were summarized by the following evaluation criteria: average estimate (Est in Table 1), standard

error (SE), bias, standardized bias (Stand Bias), root mean squared error (RMSE), 95% confidence interval (CI) coverage rate (95% cov), average width of 95% CI (AW). Standardized bias is a ratio of the bias to the empirically estimated standard errors expressed as a percentage. For example, a standardized bias of +100% means that, on average, the estimate is one standard deviation above the true parameter value. Demirtas (2004) suggests that standardized bias of less than 50% in either direction is of no significant practical importance and can be ignored.

Model S1 recognizes the bivariate nature of the data but ignores the random scale effects. Results of this model are presented in the left panel of Table 1. The estimated fixed effect parameters are unbiased with 95% CI coverage rates close to the nominal value. The random location parameters are estimated with precision and accuracy, small raw and relative bias, and 95% CI coverage close to the nominal level. The WS covariance is also estimated with high precision and accuracy. The WS variance for each outcome is modeled using log link function, but excluding the random scale effect, and the intercepts in both models are highly biased, with standardized bias of 393% and 272% for outcome 1 and 2, respectively. Despite the fact that the intercepts are precise, which is indicated by small standard errors and narrow average width of the CI, their 95% CI coverage rates are only 0.10 and 3.40 for outcome 1 and 2, respectively. The parameter estimates for the gender effect for both outcomes have good accuracy (small raw and standardized biases), but are lacking in precision (95% CI coverage rates are only 51 for positive affect and 67.7 for tired/bored). Overall, this model performs quite well in estimating the fixed and random location parameters but greatly overestimates the WS variances and provides poor inference for the covariate effects on the WS variances.

Model S2 accounts for all parameters that were used to generate the data. Results of this model can be found in the right panel of Table 1. The data are analyzed taking into account the bivariate structure by specifying BS and WS covariances, and also recognizes that the WS variances have random scale components. The fixed and random location effect covariates are estimated with high precision and accuracy. The WS variance parameters for both outcomes are estimated with small bias, less than 0.02 raw bias and less than 16% standardized bias, and with 95% CI coverage rates close to the nominal level. The random scale parameters have an approximate 88% coverage rate and slightly larger bias as compared to other model estimates. The rest of the random location and scale covariance parameters are also estimated with small biases, small RMSEs, 95% CI coverage rates close to the nominal value, and narrow average CI widths.

Additionally, to evaluate the performance of a more traditional mixed-effect model in the context of this complex data-generating scenario, we ran a set of simulations where the data were analyzed by two separate random intercepts models. The simulation results showed that fixed effect parameters for both outcomes (i.e. intercept and gender) had very small bias and close to nominal coverage. The random intercept variances were also unbiased, with coverage close to the nominal 95%, and small RMSEs. However, the error variances were appreciably biased (overestimated) although precise which was reflected in small SEs and confidence interval widths. This finding confirms that all unaccounted data variation

essentially goes into error variance. While this may not be a major concern, it would lead to biased estimates of the intraclass correlation.

6. Application to the Adolescent Smoking Study

Data for this paper come from a natural history of adolescent smoking study ("Social-Emotional Contexts of Adolescent Smoking Patterns"). Youth were enrolled after written parental consent and student assent was obtained. The sample for the current study included a subset of participants from the overall study ($N = 1263$) who provided EMA data at baseline ($N = 461$). Students were invited into the EMA study if they were former experimenters ($n = 112$), current experimenters ($n = 249$), or regular smokers ($n = 100$); thus, all participants in the current study had smoking experience. Participants ranged in age from 13.85 years to 17.29 years ($M = 15.67$ years, $SD = 0.61$), 50.7% were 9th graders, 55.1% were girls, and 56.8% White.

Data collection procedures included, among others, a week long time/event sampling via personal digital assistants (PDAs), which produced the EMA data. The EMA data collection provides many more observations per subject compared to usual longitudinal studies. Since only random prompts of the EMA data collection over several days were analyzed we were not interested in exploring temporal trends in subject responses. Adolescents carried the PDAs with them during 7 consecutive days and filled in questionnaires based on random prompts. Questions included ones about place, mood, activity, and other subjective items. There were 14,105 random prompts obtained from 461 students with an average of 30 prompts per student (range from 7 to 71).

Two outcome measures considered in the analysis were a subject's positive affect (PA) and a measure of how tired and bored (TB) they were feeling. Both of these measures consisted of the average of several mood items. Each mood item was measured on a scale of 1 to 10 with 10 representing very high level of the attribute. A total of 18 items were used to measure a subject's mood. All of the items were assessed by factor analyses that resulted in five mood measures: positive affect, negative affect, social isolation, tired and bored, and nervous and embarrassment. Higher values of positive affect indicated relatively better mood; higher values of the tired/bored measure represented relatively more tired or bored feeling.

Overall, PA had a mean of 6.8 ($SD=1.93$, median=7.0). The TB outcome had a mean of 4.72 ($SD=2.32$, median=4.67). The overall marginal correlation between the two outcomes was -0.33 , whereas the observed BS correlation for the subject-average levels of PA and TB responses was estimated to be -0.35 . A scatter plot of the subject-average outcomes is presented in Figure 1, where PA is plotted on the x-axis and TB is on the y-axis. A paired-profile graph in Figure 2 gives a more detailed picture of the average association between these outcomes for each subject. The majority of subjects have high values of weekly PA and low values of weekly TB measures. It is clear from the figure that the association between the subject outcomes is heterogeneous, such as some subjects have low weekly PA and high weekly TB. Modeling the BS heterogeneity of this response association is of interest and will provide possible explanation to the observed differences. Moreover, the

wide spread of the points on the vertical axes for both PA and TB responses indicates presence of high heterogeneity in responses at the subject level (large BS variance).

It is of interest to model the BS and WS covariance of the two outcomes in terms of covariates and examine whether covariates can explain some of the heterogeneity in these mood measures, over and above their influence on the mean responses. The model included the following sub-models: Mean of PA; Mean of TB; WS variance of PA; WS variance of TB; WS covariance; BS variance of PA; BS variance of TB; BS covariance. The following subject-level covariates collected at the baseline wave were included: grade in high school (9th or 10th grade), gender, day of the week (Friday or Saturday versus other days), negative mood regulation (a measure of the students' ability to regulate negative moods, range from 1.6 to 5, $M=3.5$), novelty seeking (a measure of the students' tendency to respond actively to new stimuli, range from 1 to 5, $M=3.5$), depression (assessed by the CES-D scale, scores ranged from 0 to 52 with an overall mean of 17.5), and smoking status (defined as smoking at least one cigarette in the past 30 days). Each model component was specified with this same set of covariates. The NMR, novelty seeking, and depression measures entered all models as continuous variables. All models were estimated using PROC NL MIXED, SAS Institute, v. 9.2. Results are presented in Table 2.

Mean of PA

Among all covariates, day of week, NMR, and the depression measure were significantly associated with the PA outcome. Subject specific PA mood was 0.11 points higher on Friday or Saturday compared to the rest of the week ($p<0.0001$). Ability to cope with negative mood was positively associated with the PA mood ($\hat{\beta} = 0.23$, $p=0.026$). More depressed students had lower PA mood ($\hat{\beta} = -0.04$, $p<0.0001$). Gender, grade, novelty seeking, and smoking were not significant predictors of the PA mood outcome.

Mean of TB

Gender was significantly associated with TB, such that male students had 0.45 points lower TB compared to female students ($p=0.001$). Day of the week was also significantly and negatively associated with TB ($\hat{\beta} = -0.26$, $p<0.0001$), namely, students were feeling less tired/bored on Friday or Saturday than the other days of the week. Higher reported NMR corresponded to lower TB ($\hat{\beta} = -0.26$, $p=0.049$). Higher values on novelty seeking were associated with higher TB ($\hat{\beta} = 0.47$, $p<0.0001$). A unit increase in the depression measure was associated with 0.04 points increase in TB ($p<0.0001$). Students who smoked during the past 30 days had higher TB by 0.30 points ($p=0.022$).

Within subject variance of PA

The WS variance for PA was modeled via a log link function, thus all coefficients (for the WS variance of PA) presented in Table 2 are on the log-scale and when converted to the original scale should be interpreted as a multiplicative effect of the covariate. Gender was a significant predictor of WS variability; male students displayed 12% more consistent PA mood behavior compared to female students ($p=0.034$). 10th grade students had less erratic PA mood compared to the 9th graders, ($p=0.026$). Students on Friday and Saturday experienced higher (by $\exp(0.131) = 1.14$ times) variation in their PA mood compared to the

other days of the week ($p < 0.0001$). Novelty seeking and depression were also associated with more erratic behavior, ($\exp(0.111) = 1.12$, $p = 0.014$ and $\exp(0.025) = 1.02$, $p < 0.0001$, respectively).

Within subject variance of TB

In contrast to PA, gender was not a significant predictor of the WS variance of TB. The 10th grade students were 10% less erratic in TB compared to 9th grade students. Consistent with the results for WS PA variance, TB feelings on Friday or Saturday were less consistent than on other days of the week, although the effect was not quite significant ($\exp(0.049) = 1.05$, $p = 0.090$). The other significant predictors of WS variance heterogeneity were novelty seeking and depression which were positively associated with higher WS variability in the TB outcome.

Random scale

Variance estimates of the random scale parameters were $\exp(-1.1789) = 0.3076$ for PA mood and $\exp(-1.7936) = 0.1664$ for TB, and both were highly significant. Expressed as standard deviations, these equal 0.5546 (PA) and 0.4079 (TB). These estimates represent the additional heterogeneity in the WS variances that is not explained by the covariates. For example, a subject with 1std above the random scale mean was 3 times more erratic in their PA mood than a subject with the same covariate values but with 1std below the random scale mean.

Among other estimated elements of the variance-covariance matrix of the random effects, it is worth mentioning that the covariance between the PA random location and scale effects was negative and significant, $\hat{\sigma}_{u(1)\omega(1)} = -0.2699$, $p < 0.0001$. Thus, subjects with higher PA mood also exhibited less variability in PA mood. For the TB outcome, the estimated covariance between the random location and scale effects was relatively small and marginally significant, ($\hat{\sigma}_{u(2)\omega(2)} = -0.2699$, $p = 0.0646$), suggesting that subjects with higher TB mean levels were also less consistent. Lastly, the covariance between PA and TB random scale terms was 0.0923 ($p < 0.0001$), indicating that subjects with more erratic PA mood were also more erratic in their TB feelings.

Within subject covariance

The association between PA mood and TB feeling within a subject was 0.148 more negative on Friday or Saturday compared to other days of the week ($p < 0.0001$). Higher values of NMR reduced this negative association (moving it closer to zero) between outcomes ($p = 0.001$). More depressed students had more negatively associated outcomes, although the magnitude of the depression effect was relatively small, ($p = 0.003$).

The WS covariance can be expressed as a correlation using the expression

$\rho_{\varepsilon_{ij}^{(1)} \varepsilon_{ij}^{(2)}} = \sigma_{\varepsilon_{ij}^{(1)} \varepsilon_{ij}^{(2)}} / \sqrt{\sigma_{\varepsilon_{ij}^{(1)}}^2 \sigma_{\varepsilon_{ij}^{(2)}}^2}$. For example, the estimated WS correlation is -0.25 for an average subject (with zero random scale effects) that is a 9th grade female with mean values of MNR, novelty seeking, and depression on weekday or Sunday. Similarly, the estimated

WS correlation is -0.24 for a 9th grade male with mean values of MNR, novelty seeking, and depression on weekday or Sunday.

Between subject variance for PA

The 10th grade students were less heterogeneous by a factor of $\exp(-0.4195) = 0.6574$ in PA mood compared to 9th graders, ($p=0.0008$). Another significant predictor was novelty seeking. It is interesting to note that the effect of novelty seeking on BS variance was opposite to its effect on WS variance. A unit increase in novelty seeking corresponded to $\exp(-0.3131) = 0.7312$ times less BS heterogeneity in the PA mood measure. Thus, novelty seekers were more alike, but also exhibited greater mood variation individually.

Between subject variance for TB

Males were marginally less heterogeneous in TB ($p=0.09$). No other predictors were found to be significant.

Between subject covariance

The BS covariance is an expression of the association between the means of the two outcomes, (i.e., averages over the repeated measurements of a subject). No significant predictors were found.

Similar to the WS covariance, the BS covariance can be expressed as correlation using the

expression $\rho_{u_i^{(1)} u_i^{(2)}} = \sigma_{u_i^{(1)} u_i^{(2)}} / \sqrt{\sigma_{u_i^{(1)}}^2 \sigma_{u_i^{(2)}}^2}$. For example, the estimated BS correlation is -0.26 for a 9th grade female with mean values of MNR, novelty seeking, and depression on weekday or Sunday, while it equals -0.33 for a similar male.

Residual analysis was used to evaluate the model diagnostics. Histograms of the raw conditional residuals did not reveal any systematic departure from a normal distribution for both outcomes. Scatter plots of the raw conditional residuals versus fitted values demonstrated that the residuals have approximate homogeneous variance. A kernel density of the bivariate conditional residuals showed reasonable agreement with a bivariate normal distribution.

7. Discussion

This article has illustrated how mixed-effects models for bivariate EMA data with clustered observations can be used to jointly model BS and WS covariances as well as heterogeneity in BS and WS variances, in addition to modeling mean levels of the outcomes. As such, these models can help to identify predictors of both WS and BS covariation as well as WS and BS variation and to test hypotheses about these covariances and variances. Additionally, by including random subject effects on the WS variances, this model can examine the degree to which subjects are heterogeneous beyond the differences explained by covariates. The joint model for bivariate outcomes specifies the mean structure as a random-intercept linear model and also models variation and cross-covariance of the random effects and subject's measurement errors in terms of covariates. Conditional subject measurement errors are

independent of the random location and scale effects, whereas the random location and scale effects are allowed to be correlated.

A simulation study showed the model is reliable in recovering the true parameter values with good precision and accuracy. Data were simulated with close resemblance to the real data and were analyzed by two models. The models differed in their estimation of random scale parameters. Both models performed well in recovering the true values for most of the parameters, but differed in terms of the error variance parameters. As might be expected, the model without random scale parameters overestimated the intercept values of the error terms for both outcomes, and provided poor coverage for the covariate effects on the WS variances. The model with random scale parameters corrected these problems.

The application of this method to real data (and its estimation using SAS PROC NLMIXED) has illustrated its practical usefulness. We explored whether covariates were related to the means and variances (both BS and WS) for two outcomes, PA and TB. These outcomes are important constructs in studying adolescent mood and have been analyzed in this context separately elsewhere. An advantage of the proposed model is that it allows studying PA and TB association by means of covariates. The overall covariance was separated out into between- and within-subject components. Here, the estimated BS covariance, the association between subject-average responses, was negative; higher subject-average PA was associated with lower subject-average TB. The estimated WS covariance was also negative and varied by day of week, NMR, and depression. The WS association of the two outcomes was stronger (more negative) on Friday or Saturday than during weekdays or on Sunday. Higher negative mood regulation was associated with diminished WS negative association of the two outcomes.

In addition to modeling WS and BS association, WS and BS variation in the outcomes were explored. WS variability reflects subject's inconsistency in responses. We found that males were more consistent in their PA responses than females. In terms of BS variability, grade and novelty seeking were significant for PA, whereas BS variability in TB was only marginally significantly different with gender.

Since the normal distribution for the random scale effects was assumed, the model can be implemented in PROC NLMIXED, SAS Institute, v.9.2, and therefore broadens the potential application of this approach. Sample syntax is included in the appendix. The current model specified random scale effects for the WS variances. A possible extension of the model might also include random effects into the model of the WS covariance. The notion being that the WS association of the two outcomes could vary at the individual level. Also, the two measures were modeled here as continuous variables. A natural extension would be to develop the model for ordinal outcomes. When temporal trends among the repeated observations are of interest, the proposed model can be extended to include random trends to the mean models to account for serial dependence in the outcomes.

Selection of a model among a set of competing models can follow a general two-step procedure (Hedeker and Gibbons 2006, page 129). First, including all fixed effects, parameters of the variance-covariance matrices of the random effects and error terms are

selected. Second, given the selected covariance structure for the model, one can proceed in selection of significant covariates for the mean models. Since model estimation is based on maximum likelihood and sample sizes are generally large, the likelihood ratio test for nested models as well as AIC or BIC model selection criteria can be used. AIC and BIC are applicable in a broad array of modeling frameworks, since their large-sample justification only requires conventional asymptotic properties of maximum likelihood estimators (Akaike 1973; Schwarz 1978).

Modeling of variances and covariances requires a fair amount of data. The EMA data collection provides large numbers of repeated observations that can be used for these purposes. However, modeling of the variance-covariance matrix of the outcomes in the proposed model can be computationally challenging. In some case, the estimation procedure might not converge due to various reasons (e.g., a non-positive definite variance-covariance matrix). To resolve computational issues a simpler model with fewer parameters should be used in these cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCE LIST

- Aitkin M. Modelling Variance Heterogeneity in Normal Regression Using GLIM. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*. 1987; 36:332–339.
- Akaike, H. Information Theory and an Extension of the Maximum Likelihood Principle. In: Petrov, BN.; Csaki, F., editors. 2nd International Symposium on Information Theory. Budapest: Akademiai Kiado; 1973. p. 267-281.
- Balazs K, Hidegkuti I, De Boeck P. Detecting Heterogeneity in Logistic Regression Models. *Applied Psychological Measurement*. 2006; 30:322–344.
- Bolger N, Davis A, Rafaeli E. Diary Methods: Capturing Life as it is Lived. *Annu. Rev. Psychol.* 2003; 54:579–616. [PubMed: 12499517]
- Burton A, Altman DG, Royston P, Holder RL. The design of simulation studies in medical statistics. *Statist. Med.* 2006; 25:4279–4292.
- Carroll RJ. Variances Are Not Always Nuisance Parameters. *Biometrics*. 2003; 59:211–220. [PubMed: 12926705]
- Daniels MJ, Zhao YD. Modelling the random effects covariance matrix in longitudinal data. *Statistics in Medicine*. 2003; 22:1631–1647. [PubMed: 12720301]
- Demirtas H. Simulation driven inferences for multiply imputed longitudinal datasets. *Statistica Neerlandica*. 2004; 58:466–482.
- Elliott M. Identifying latent clusters of variability in longitudinal data. *Biostatistics*. 2007; 8:756–771. [PubMed: 17267391]
- Fowler K, Whitlock MC. The Distribution of Phenotypic Variance with Inbreeding. *Evolution*. 1999; 53:1143–1156.
- Ghosh P, Tu W. Assessing Sexual Attitudes and Behaviors of Young Women: A Joint Model with Nonlinear Time Effects, Time Varying Covariates, and Dropouts. *Journal of the American Statistical Association*. 2008; 103:1496–1507. [PubMed: 19300533]

- Harvey AC. Estimating Regression Models with Multiplicative Heteroscedasticity. *Econometrica*. 1976; 44:461–465.
- Hedeker D, Berbaum ML, Mermelstein R. Location-scale models for multilevel ordinal data: Between- and within-subjects variance modeling. *Journal of Probability and Statistical Science*. 2006; 4:1–20.
- Hedeker, D.; Gibbons, RD. *Longitudinal Data Analysis*. John Wiley & Sons; 2006.
- Hedeker, D.; Mermelstein, R. Mixed-effect regression models with heterogeneous variance: Analyzing ecological momentary assessment data of smoking. In: Little, TD.; Bovaird, JA.; Card, NA., editors. *Modeling Ecological and Contextual Effects in Longitudinal Studies of Human Development*. Mahwah, NJ: Erlbaum; 2007. p. 183–206.
- Hedeker D, Mermelstein RJ, Demirtas H. An application of a mixed-effects location scale model for analysis of Ecological Momentary Assessment (EMA) data. *Biometrics*. 2008; 64:627–634. [PubMed: 17970819]
- Hubbard RA, Inoue LYT, Diehr P. Joint Modeling of Self-Rated Health and Changes in Physical Functioning. *Journal of the American Statistical Association*. 2009; 104:912–928. [PubMed: 20151036]
- Inoue LYT, Etzioni R, Morrell C, Muller P. Modeling Disease Progression With Longitudinal Markers. *Journal of the American Statistical Association*. 2008; 103:259–270. [PubMed: 24453387]
- Laird NM, Ware JH. Random-Effects Models for Longitudinal Data. *Biometrics*. 1982; 38:963–974. [PubMed: 7168798]
- Pourahmadi M. Maximum likelihood estimation of generalised linear models for multivariate normal covariance matrix. *Biometrika*. 2000; 87:425–435.
- Pourahmadi M, Daniels MJ. Dynamic Conditionally Linear Mixed Models For Longitudinal Data. *Biometrics*. 2002; 58:225–231. [PubMed: 11890319]
- Reno R, Rizza R. Is Volatility Lognormal? Evidence from Italian futures. *Physica A: Statistical Mechanics and its Applications*. 2003; 322:620–628.
- Schwarz G. Estimating the dimension of a model. *Annals of Statistics*. 1978:461–464.
- Shenk TM, White GC, Burnham KP. Sampling-variance effects on detecting density dependence from temporal trends in natural populations. *Ecological Monographs*. 1998; 68:445–463.
- Sithole JS, Jones PW. Bivariate Longitudinal Model for Detecting Prescribing Change in Two Drugs Simultaneously with Correlated Errors. *Journal of Applied Statistics*. 2007; 34:339–352.
- Verbeke G, Lesaffre E. The effect of misspecifying the random-effects distribution in linear mixed models for longitudinal data. *Computational Statistics & Data Analysis*. 1997; 23:541–556.
- Zhang D, Davidian M. Linear Mixed Models With Flexible Distributions Of Random Effects For Longitudinal Data. *Biometrics*. 2001; 57:795–802. [PubMed: 11550930]

Figure 1.
Subject-average association between PA and TB measures, N=461

Figure 2.
Paired profile of subject-average PA and TB measures

Table 1

Results for data simulated from a bivariate mixed-effects location-scale model with correlated random location and scale effects and correlated errors. 461 subjects with 30 measurements per subject.

S1: Bivariate Mixed-Effects Model with Correlated Random Location Effects and Correlated Errors			S2: Bivariate Mixed-Effects Location-Scale Model with Correlated Random Location and Scale Effects and Correlated Errors													
Component	Parameter	True Value	Est	SE	Bias	Stand Bias	RMSE	95% cov	AW	Est	SE	Bias	Stand Bias	RMSE	95% cov	AW
Fixed Effect covariates																
Outcome 1	Intercept	6.654	6.655	0.081	0.0015	1.8460	0.081	93.00	0.306	6.655	0.080	0.0014	1.8058	0.080	93.12	0.305
	GenderM	0.280	0.278	0.119	-0.0016	-1.3411	0.119	93.80	0.456	0.279	0.118	-0.0009	-0.7999	0.118	93.52	0.454
Outcome 2	Intercept	5.085	5.090	0.097	0.0052	5.3752	0.097	95.00	0.382	5.089	0.097	0.0041	4.1928	0.097	94.84	0.381
	GenderM	-0.765	-0.777	0.142	-0.0120	-8.4508	0.142	95.80	0.570	-0.776	0.142	-0.0107	-7.5118	0.142	95.85	0.568
Error terms																
$\log\left(\sigma_{\varepsilon_{ij}}^{2(1)}\right)$	Intercept	0.736	0.918	0.046	0.1816	393.4558	0.187	0.10	0.063	0.757	0.128	0.0205	15.9931	0.130	92.11	0.160
	GenderM	-0.216	-0.218	0.067	-0.0015	-2.2343	0.067	51.00	0.092	-0.215	0.061	0.0006	0.9343	0.061	95.75	0.237
$\log\left(\sigma_{\varepsilon_{ij}}^{2(2)}\right)$	Intercept	1.071	1.162	0.033	0.0907	272.7621	0.097	3.40	0.063	1.088	0.112	0.0166	14.7532	0.113	91.19	0.122
	GenderM	0.000	0.001	0.049	0.0009	1.7797	0.049	67.60	0.092	0.000	0.047	0.0003	0.5459	0.047	94.23	0.180
$\sigma_{\varepsilon_{ij}}^{(1),(2)}$		-0.590	-0.589	0.025	0.0012	4.7167	0.025	94.00	0.093	-0.608	0.132	-0.0184	-13.9291	0.133	92.71	0.075
Random Location parameters																
$\log\left(\sigma_{u_i}^{2(1)}\right)$	Intercept	0.384	0.374	0.093	-0.0096	-10.3441	0.093	95.00	0.369	0.368	0.087	-0.0156	-17.7994	0.089	94.33	0.339
	GenderM	0.00	-0.003	0.143	-0.0025	-1.7651	0.143	94.80	0.547	-0.004	0.121	-0.0035	-2.9030	0.121	93.93	0.441
$\log\left(\sigma_{u_i}^{2(2)}\right)$	Intercept	0.833	0.826	0.092	-0.0071	-7.7873	0.092	96.30	0.365	0.821	0.093	-0.0116	-12.5466	0.093	94.64	0.359
	GenderM	0.000	0.003	0.144	0.0027	1.9106	0.144	94.10	0.545	-0.008	0.147	-0.0078	-5.2728	0.147	93.22	0.521
$\sigma_{u_i}^{(1),(2)}$	Intercept	-0.59	-0.585	0.122	0.0052	4.2630	0.122	95.00	0.497	-0.551	0.229	0.0388	16.9741	0.232	92.31	0.476

S1: Bivariate Mixed-Effects Model with Correlated Random Location Effects and Correlated Errors										
Component	Parameter	True Value	Est	SE	Bias	Stand Bias	RMSE	95% cov	AW	
S2: Bivariate Mixed-Effects Location-Scale Model with Correlated Random Location and Scale Effects and Correlated Errors										
Random Location Effects and Correlated Errors										
Random scale parameters										
$\log\left(\sigma^2_{\omega_i^{(1)}}\right)$	GenderM	0.000	-0.006	0.187	-0.0057	-3.0505	0.187	94.60	0.742	-0.008
		-1.011								-1.037
$\log\left(\sigma^2_{\omega_i^{(2)}}\right)$		-1.691								-1.722
										0.136
$\sigma_{\omega_i^{(1)}\omega_i^{(2)}}$		0.115								0.116
										0.038
Random location (u) and random scale (w) covariance										
$\sigma_{u_i^{(1)}\omega_i^{(1)}}$		-0.335								-0.328
										0.045
$\sigma_{u_i^{(1)}\omega_i^{(2)}}$		0.000								0.001
										0.029
$\sigma_{u_i^{(2)}\omega_i^{(1)}}$		-0.089								-0.087
										0.052
$\sigma_{u_i^{(2)}\omega_i^{(2)}}$		0.114								0.113
										0.038

The evaluation criteria are as follows: Est=estimate, SE=standard error, Stand Bias=standardized bias, RMSE=root mean squared error, 95% COV=95% CI coverage, AW=average width

Table 2

Parameter Estimates of the Bivariate Mixed-effects Location-Scale Model

Parameter	Positive Affect (PA)			Tired/Bored Feeling (TB)		
	Estimate	Std Err	p-value	Estimate	Std Err	p-value
<i>Fixed Effect covariates</i>						
Intercept	6.217	0.530	<.0001	3.481	0.655	<.0001
Male	0.026	0.104	0.801	-0.451	0.130	0.001
10 th grade	0.005	0.104	0.960	-0.013	0.125	0.916
Friday or Saturday	0.114	0.025	<.0001	-0.264	0.032	<.0001
NMR (cont)	0.225	0.101	0.026	-0.260	0.129	0.049
Novelty seeking (cont)	0.125	0.080	0.118	0.448	0.095	<.0001
Depression (cont)	-0.038	0.007	<.0001	0.039	0.009	<.0001
Smoke in past 30 days	-0.103	0.105	0.325	0.303	0.132	0.022
<i>WS variance (log scale)</i>						
Intercept	-0.264	0.302	0.381	0.330	0.238	0.167
Male	-0.129	0.061	0.034	-0.012	0.048	0.799
10 th grade	-0.130	0.058	0.026	-0.099	0.046	0.033
Friday or Saturday	0.131	0.029	<.0001	0.049	0.029	0.090
NMR (cont)	0.054	0.059	0.361	0.026	0.047	0.583
Novelty seeking (cont)	0.110	0.045	0.014	0.148	0.035	<.0001
Depression (cont)	0.025	0.004	<.0001	0.008	0.003	0.014
Smoke in past 30 days	-0.011	0.059	0.857	0.049	0.047	0.296
<i>BS variance (log scale)</i>						
Intercept	0.822	0.585	0.160	0.976	0.832	0.241
Male	-0.041	0.125	0.741	-0.261	0.154	0.090
10 th grade	-0.420	0.124	0.001	-0.059	0.145	0.685
Friday or Saturday	-0.186	0.158	0.239	0.009	0.174	0.960
NMR (cont)	0.122	0.121	0.313	-0.054	0.166	0.747
Novelty seeking (cont)	-0.313	0.089	0.001	0.042	0.112	0.705
Depression (cont)	0.016	0.008	0.044	-0.009	0.011	0.398

Positive Affect (PA)				Tired/Bored Feeling (TB)			
Parameter	Estimate	Std Err	p-value	Estimate	Std Err	p-value	
Smoke in past 30 days	-0.031	0.120	0.793	-0.240	0.148	0.105	
<i>Random scale variance (log scale)</i>							
	-1.179	0.081	<.0001	-1.794	0.093	<.0001	
Parameter	Estimate	Std Err	p-value				
<i>WS covariance of PA and TB</i>							
Intercept	-0.853	0.207	<.0001				
Male	0.070	0.041	0.090				
10 th grade	0.068	0.041	0.096				
Friday or Saturday	-0.148	0.036	<.0001				
NMR (cont)	0.138	0.042	0.001				
Novelty seeking (cont)	-0.025	0.031	0.420				
Depression (cont)	-0.009	0.003	0.003				
Smoke in past 30 days	-0.034	0.040	0.404				
<i>BS covariance of PA and TB</i>							
Intercept	-0.817	0.792	0.303				
Male	-0.034	0.137	0.806				
10 th grade	0.039	0.140	0.780				
Friday or Saturday	0.106	0.156	0.498				
NMR (cont)	-0.034	0.159	0.830				
Novelty seeking (cont)	0.084	0.103	0.412				
Depression (cont)	0.009	0.009	0.324				
Smoke in past 30 days	0.194	0.136	0.155				
<i>Random location (u) and random scale (w) covariance</i>							
$\sigma_{\omega(PA),\omega(TB)}$	0.092	0.015	<.0001				
$\sigma_{u(PA),\omega(PA)}$	-0.270	0.033	<.0001				
$\sigma_{u(TP),\omega(PA)}$	-0.015	0.039	0.700				

Parameter	Estimate	Std Err	p-value
$\sigma_{u(PA),\omega(TB)}$	-0.006	0.024	0.812
$\sigma_{u(TP),\omega(TB)}$	0.058	0.031	0.065