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A Joint Marginal-Conditional Model for Multivariate Longitudinal Data

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Abstract

Multivariate longitudinal data frequently arise in biomedical applications, however their analyses are often carried out one outcome at a time, or jointly using existing software in an *ad hoc* fashion. A main challenge in the proper analysis of such data is the fact that the different outcomes are measured on different unknown scales. Methodology for handling the scale problem has been previously proposed for cross-sectional data, and here we extend it to the longitudinal setting. We consider modeling the longitudinal data using random effects, while leaving the joint distribution of the multiple outcomes unspecified. We propose an estimating equation together with an EM-type (ES) algorithm. The consistency and the asymptotic distribution of the parameter estimates are established. The method is evaluated using extensive simulations, and applied to a longitudinal nutrition data set from a large dietary intervention trial on breast cancer survivors, the Women's Healthy Eating and Living (WHEL) Study.

Keywords

common effect; ES algorithm; generalized estimating equations; random effects; scaling

1 Introduction

Multivariate outcome data are increasingly common in biomedical research; for example, in toxicology studies¹, in Alzheimer's disease², and in lifestyle intervention trials targeting multiple health behaviors. As a specific example, the Women's Healthy Eating and Living (WHEL) Study was a randomized dietary intervention trial conducted in early stage breast cancer survivors between 1996 and 2006^{3,4}. Rather than target a specific nutrient, the study aimed to improve overall dietary pattern by teaching intervention participants to consume a high-fiber, low-fat diet emphasizing vegetables and fruits rich in carotenoids and other potentially protective phytochemicals. Detailed information on dietary intake of fruits, vegetables, fiber, fat, and other food components were collected at study entry, and 1 and 4-

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years post-randomization. A major goal of the study was to examine concomitant changes over time in the multivariate outcome comprising vegetable, fiber, and fat intake, which were key targets of the behavioral intervention.

Like the WHEL study, it is increasingly common to collect multivariate data repeatedly over time. While statistical methods for analyzing longitudinal data have been well studied and broadly applied^{5,6}, the analysis of multiple outcomes longitudinal data is often carried out by analyzing one outcome at a time⁷. However, in some applications the scientific question of interest concerns the multiple outcomes as a whole, as studied in Sammel et al.⁸ as well as in the WHEL study. While a primary comparison in a randomized study may compare the multiple outcomes at a final fixed time point using tests like Hotelling's T , it is often also useful to develop regression models for the longitudinal data simultaneously for all the outcomes in order to answer other questions of interest; for example, whether an intervention has an effect on rates of change for multiple outcomes. In this case, analyzing one outcome at a time can lead to multiple testing of the null hypotheses of no change in each outcome. Joint modeling, on the other hand, provides a natural framework for such tests. In addition, as we will elaborate below, through scaling to a common (unit) error variance, one can test the hypothesis of whether the intervention has a common effect on the multiple outcomes in terms of numbers of error standard deviation, which is often referred to as 'effect size'. A common effect can be of practical interest in applications, as well as potentially reduce the number of degrees of freedom, thereby increasing power, when testing against a null common effect⁹. In many observational studies it is also imperative to adjust for confounders as covariates. In this paper, we propose a general regression framework for multivariate longitudinal data that has useful interpretations in practice.

To be more specific, the correlation among the different outcomes is typically considered a nuisance, or of secondary interest. In addition, parameter estimates can be sensitive to misspecification of the correlation structure if we choose to explicitly model that¹⁰. Because of these considerations, we propose to model the different outcomes marginally and use an approach that is similar to the generalized estimating equations¹¹. On the other hand, practitioners are often accustomed to random effects modeling of the longitudinal aspect of the data, which gives interpretations such as random intercepts and slopes, and latent trends and evolutions⁷. Therefore we propose to combine the marginal and the conditional (random effects) approaches: marginal for the multivariate aspect, and conditional for the longitudinal aspect.

While the marginal approach and the conditional approach are both well-known in the correlated data literature, the combination of the two has not been widely used in practice. Here we consider the specific problem of multiple continuous outcomes measured on different unknown scales, i.e. with different error variances, this typically being the case for multiple outcomes in practice⁸. When these multiple outcomes are measured repeatedly over time, a commonly seen *ad hoc* approach is to fit a large random effects model to account for both the correlation across different outcomes and over time. A limitation of this approach lies in the handling of the different unknown error variances, when the practitioner simply scales each outcome using its sample variance, as opposed to its error variance. In addition, proper scaling can facilitate the estimation of a common effect of an exposure on different

outcomes. As an example in the WHEL data mentioned earlier, fat and fiber were measured in grams while vegetable intake was measured in servings. One way to ‘standardize’ the different outcomes is to scale them so that they all have standard normal regression errors, that is, the exposure has the effect of a location shift (after possibly controlling for other covariates) of a standard normal distribution on each outcome^{8,9}. This then forms the basis of assessing and estimating a common exposure effect, as we will further elaborate.

Inference under such a combined modeling approach carries the same combined characteristics. Since the data generating mechanism is not completely specified, likelihood based approaches are not possible. Instead estimating equations are well studied under the marginal model, albeit here with the addition of the unobserved random effects; more details are given in the following sections. This turns out to be the case of the estimating equations with missing data problem considered in Elashoff and Ryan¹², for which they developed an expectation-substitution (ES) algorithm. The ES algorithm generalizes the expectation-maximization (EM) algorithm which is applied to the log-likelihood function. We show that under our proposed model, the estimating equations together with the ES algorithm give consistent and asymptotically normally distributed estimates of the parameters.

In the next section we describe the proposed model and inference procedure. We derive the asymptotic properties of the estimator in Section 3. Finite sample properties are studied through simulations in Section 4, including its performance under misspecified correlation structures, as well as non-normally distributed errors. We apply the approach to the WHEL nutrition data in Section 5, followed by considerations of extending the approach under variations of the assumed model, and conclude with some discussion for future work.

2 Model and Estimation

2.1 The model

Let y_{ijt} represent the value of outcome j measured on subject i at time t ($i = 1, \dots, N, j = 1, 2, \dots, J, t = 1, \dots, n_j$). We assume that the y_{ijt} 's are correlated across outcomes and over time. Let x_{ijt} be a $p_j \times 1$ vector of covariates for subject i at time t and outcome j , including possibly an ‘1’ for intercept. As in many applications, we would like to model the longitudinal data using random effects models with possibly random intercepts and slopes, etc., but would like to leave the correlation among the different outcomes unspecified. So let

$$y_{ijt} = x_{ijt}^\top \beta_j + z_{ijt}^\top b_{ij} + e_{ijt}, \quad (1)$$

where β_j is a $p_j \times 1$ vector of fixed effects, b_{ij} is a $q_j \times 1$ vector of random effects for individual i and outcome j , and the corresponding covariates with random effects are denoted by z_{ijt} .

We let $\text{Var}(e_{ijt}) = \sigma_j^2$ for outcome j , $E(b_{ij}) = 0$ and $\text{Var}(b_{ij}) = D_j$. For the development below, we first assume that $\text{Cor}(b_{ij}, b_{ik}) = 0$ for any $j \neq k$, and that $\text{Cor}(e_{ijt}, e_{iks}) = 0$ for any $t \neq s$. Extensions to these assumptions are discussed in Section 6.

For a given outcome j , model (1) is a Laird and Ware¹³ type model for longitudinal data, although we do not assume normality of the random effects or errors. For multiple outcomes, a challenge in fitting model (1) is the unknown different variances σ_j^2 , sometimes referred to as scales⁹. A naive approach in some applications has been to scale each outcome by the sample variance of the y 's for that outcome, and then fit a general linear mixed-effects model with common error variance and certain correlation structure¹⁴, which can be done using existing software such as the *lme4* package in R. It is clear, however, that the quantities which ought to be used to scale the outcomes are the σ_j 's, not the variances of y .

In order to carry out proper inference, it is advantageous⁹ to consider the scaled version of (1):

$$\frac{y_{ijt}}{\sigma_j} = x_{ijt}^\top \tilde{\beta}_j + z_{ijt}^\top \tilde{b}_{ij} + e_{ijt}, \quad (2)$$

where $\tilde{\beta}_j$, $\tilde{b}_{ij}$, and $\tilde{e}_{ijt}$ here are the scaled counterparts of β_j , b_{ij} , and e_{ijt} in (1). Also, let $\text{Var}(\tilde{b}_{ij}) = \tilde{D}_j$. Model (2) also has potential applications in estimating a common effect on the different outcomes; see Section 2.3 for more details.

2.2 Estimating equations and the ES algorithm

Under model (1) denote θ the vector of parameters consisting of $\beta = (\beta_1^\top, \beta_2^\top, \dots, \beta_J^\top)^\top$, the unique entries of the D_j 's, and the σ_j 's. Denote

$y_{it}^* = (y_{i1t}/\sigma_1, \dots, y_{iJt}/\sigma_J)^\top$, $\tilde{b}_i = (\tilde{b}_{i1}^\top, \dots, \tilde{b}_{iJ}^\top)^\top$, $X_{it} = \text{diag}(x_{i1t}^\top, \dots, x_{iJt}^\top)$, and $Z_{it} = \text{diag}(z_{i1t}^\top, \dots, z_{iJt}^\top)$. Also denote $y_i^* = (y_{i1}^*, \dots, y_{in_i}^*)^\top$, $X_i = \text{stack}(X_{i1}, \dots, X_{in_i})$ is a $n_i J \times (\sum_j p_j)$ matrix and where 'stack' is to put submatrices on top of each other in order, and $Z_i = \text{stack}(Z_{i1}, \dots, Z_{in_i})$ is a $n_i J \times (\sum_j q_j)$ matrix. Finally we write $\tilde{e}_{it}$ and $\tilde{e}_j$ as the corresponding error vectors of y_{it}^* and y_i^* , respectively.

To estimate θ , we first consider conditioning on the random effects. Based on the general estimating equations (GEE) approach, we have

$$\sum_{i=1}^N \mathcal{Q}_i^{(1)}(\theta) = \sum_{i=1}^N \sum_{t=1}^{n_i} X_{it}^\top R^{-1} (y_{it}^* - X_{it} \tilde{\beta} - Z_{it} \tilde{b}_i) = 0, \quad (3)$$

$$\sum_{i=1}^N \mathcal{Q}_i^{(2)}(\theta) = \sum_{i=1}^N \left[\sum_{t=1}^{n_i} \left\{ \frac{y_{ijt}}{\sigma_j} \left(\frac{y_{ijt}}{\sigma_j} - x_{ijt}^\top \tilde{\beta}_j - z_{ijt}^\top \tilde{b}_{ij} \right) - 1 \right\} \right]_{j=1, \dots, J} = 0, \quad (4)$$

$$\sum_{i=1}^N \mathcal{U}_i^{(3)}(\theta) = \sum_{i=1}^N [\tilde{b}_{ij} \tilde{b}_{ij}^\top - \tilde{D}_j]_{j=1, \dots, J} = 0, \quad (5)$$

where $[a_j]_{j=1, \dots, J} = (a_1, \dots, a_J)^\top$. In the above R is the working correlation matrix of the error vector $\tilde{e}_{it}$, just like in the GEE. The first set of estimating equations (3) are unbiased

regardless of whether R is misspecified; note that $E\{\sum_{i=1}^N \mathcal{U}_i^{(1)}(\theta) | \tilde{b}_1, \dots, \tilde{b}_N\} = 0$ implies $E\{\sum_{i=1}^N \mathcal{U}_i^{(1)}(\theta)\} = 0$. In addition, (3) is known to be efficient when R is correctly specified and there are no random effects. The second set of equations (4) are method-of-moments equations for σ_j^2 , and more details are given in the Appendix. Similar equations like (3) and (4) were also used in Roy et al.⁹. The third set (5) are method-of-moments equations for the unstructured D_j 's, noting that the b_{ij} 's are assumed to have mean zero. If one decides to use a different parametrization for D_j other than unstructured, for example independent random intercept and slope, corresponding equations can be written down similarly.

Elashoff and Ryan¹² developed an ES algorithm for general estimating equations with missing data, in a way similar to the EM algorithm for maximum likelihood estimation. Typically the estimating equations are derived for complete data or, in other words, conditional on the missing data. The ES approach takes the conditional expectation of the complete data estimating equation given the observed data, and iterates between an E-step and a S-step, where the expected values of the missing data sufficient statistics under current parameter values are substituted in to update the unknown parameters. The approach is very similar to the EM algorithm, except that it operates on the estimating equations instead of the log-likelihoods. In the following we adapt the ES approach to our equations above.

E-step—Denote $\mathcal{U}_i(\theta) = (\mathcal{U}_i^{(1)}(\theta)^\top, \mathcal{U}_i^{(2)}(\theta)^\top, \mathcal{U}_i^{(3)}(\theta)^\top)^\top$, then we have $\sum_{i=1}^N \mathcal{U}_i(\theta) = 0$. To take the conditional expectations of $\mathcal{U}_i(\theta)$ given y_i , where y_i is the vector of outcome y_{ijt} 's for individual i , we need $E(\tilde{b}_i | y_i)$ and $E(\tilde{b}_i \tilde{b}_i^\top | y_i)$. The ES approach allows separate modeling of the missing data mechanism which, in our case, is the modeling of these two conditional expectations. Motivated by the conditional moments under the multivariate normal distribution, we consider

$$\begin{aligned} E(\tilde{b}_i | y_i^*) &= (\tilde{D} Z_i^\top) (Z_i \tilde{D} Z_i^\top + R^*)^{-1} (y_i^* - X_i \tilde{\beta}), \\ \text{Var}(\tilde{b}_i | y_i^*) &= \tilde{D} - (\tilde{D} Z_i^\top) (Z_i \tilde{D} Z_i^\top + R^*)^{-1} (\tilde{D} Z_i^\top)^\top, \end{aligned} \quad (6)$$

where $\tilde{D} = \text{Cov}(\tilde{b}) = \text{diag}(\tilde{D}_1, \dots, \tilde{D}_J)$ is a $(\sum_j q_j) \times (\sum_j q_j)$ matrix, and R^* is a $n_i J \times n_i J$ error covariance matrix whose elements corresponding to $\text{Cov}(e_{ijt}, e_{ij't'})$ are given by the corresponding elements of the working correlation matrix R . It is clear that

$E(\tilde{b}_i \tilde{b}_i^\top | y_i^*) = \text{Var}(\tilde{b}_i | y_i^*) + E(\tilde{b}_i | y_i^*) E(\tilde{b}_i | y_i^*)^\top$. We emphasize that we only assume the

moments condition in (6) and do not assume normality. In the simulations we will examine the above inference procedure for non-normal data.

S-step—To carry out the ES algorithm, one provides the initial values for all the parameters. We found it advantageous to use the estimate of σ_j by fitting a linear mixed model as in (1) to outcome j alone as its initial value. In our algorithm, values of θ are updated by substituting $\tilde{b}_{ij}$ and $\tilde{b}_{ij}\tilde{b}_{ij}^\top$ in $\sum_{i=1}^N \mathcal{U}_i(\theta)$ with their conditional expectations according to (6), where the expectations are evaluated under the current parameter values. In the S-step:

1. The first set of equations (3) can be solved using existing GEE software. In this case following the E-step, $y_{it}^* - Z_{it}E(\tilde{b}_i|y_i)$ are the ‘outcomes’ for fitting the GEE here, and X_{it} are the predictors, the working correlation is given by R , and the ‘clusters’ are formed by the J outcomes within each subject i and time t ; in other words, different time points within a subject are treated as independent for this part of the S-step.
2. Each equation in (4) is a quadratic equation in $1/\sigma_j$ of the form $ax^2+bx+c=0$, and can be solved algebraically using the well-known quadratic formula. It is straightforward to verify here that $a=\sum_{i,t} y_{ijt}^2 > 0$ and $c = -\sum_i n_i < 0$, therefore the equation has one positive and one negative root; the positive root is retained for the update of σ_j in the S-step.
3. Finally, equation (5) is written assuming that D_j is unstructured and can be easily solved as $\tilde{D}_j = \sum_{i=1}^N E(\tilde{b}_{ij}\tilde{b}_{ij}^\top|y_i)/N$. If a different parametrization for D_j is used, the corresponding equations can also be solved accordingly.

The convergence of the ES algorithm was discussed in Elashoff and Ryan¹², with references to general theory on iterative solutions to nonlinear equations by Ortega and Rheinboldt¹⁵ and Ortega¹⁶, and is not pursued further here.

2.3 Testing and estimation of a common effect

Consider w_{it} an exposure of particular interest, then model (2) can be written as

$$\frac{y_{ijt}}{\sigma_j} = w_{it}\alpha_j + x_{ijt}^\top \tilde{\beta}_j + z_{ijt}^\top \tilde{b}_{ij} + \tilde{e}_{ijt}, \quad (7)$$

where x_{ijt} denotes the rest of the covariates. The following submodel might be of interest, which assumes a common effect α of w_{it} on all outcomes:

$$\frac{y_{ijt}}{\sigma_j} = w_{it}\alpha + x_{ijt}^\top \tilde{\beta}_j + z_{ijt}^\top \tilde{b}_{ij} + \tilde{e}_{ijt}. \quad (8)$$

It is possible to test model (8) versus (7). We show in the next section that $(\hat{a}_1, \dots, \hat{a}_J)^\top$ is asymptotically multivariate normal with variance-covariance matrix estimated by a sandwich estimator. We can then test $H_0: a_1 = \dots = a_J$ using the $J-1$ contrasts $(a_1 - a_2, \dots, a_1 - a_J)^\top$, whose estimates are also jointly normal with variance that can be calculated from that of $(\hat{a}_1, \dots, \hat{a}_J)^\top$. Therefore the hypothesis of a common (scaled) effect can be tested using a Wald test with $J-1$ degrees of freedom. Similarly a subset of the a 's can be tested for equality, as we illustrate using the WHEL data later.

If the null hypothesis in the above is not rejected, model (8) can be fitted using the ES approach described above by formulating a proper design matrix for the fixed effects; conversely β_j under the more general model (1) (or $\tilde{\beta}_j$ under (2)) can be seen as the interaction effect between x_{ijt} and the indicator for outcome j . In addition to the interpretation of a common effect, an advantage of using model (8) to test $a = 0$ is a more powerful χ^2_1 asymptotic test as opposed to χ^2_J under model (1) or (2).

3 Asymptotic Properties

To study the asymptotic properties of $\hat{\theta}$ obtained using the ES approach, it is important to recognize that at convergence of the algorithm $\hat{\theta}$ solves the unconditional estimating

equations $\sum_{i=1}^N U_i(\theta) = 0$, where $U_i = E_{\theta}\{\mathcal{U}_i(\theta) | y_i\}$. Given the closed form expressions of the conditional expectations in (6), one can explicitly write down the expressions for U_i and these are given in the Appendix.

From the expression in the Appendix it is clear that $U_i(\theta)$ is continuously differentiable with respect to θ , denote the first order Jacobian matrix $U'_i(\theta) = \partial U_i(\theta) / \partial \theta$. We make the following assumptions:

- i. The triples (y_i, X_i, Z_i) , $i = 1, \dots, N$, are independent and identically distributed with finite first and second moments, and satisfy models (1) and (6);
- ii. There is a neighborhood of θ_0 on which $\sum_{i=1}^N U'_i(\theta) / N$ converges uniformly to $E\{U'_i(\theta)\}$ in probability as $N \rightarrow \infty$;
- iii. $E\{U'_i(\theta_0)\}$ is non-singular.

We have the following.

Theorem 1—Under conditions i. – iii. above, $\sum_{i=1}^N U_i(\theta) = 0$ has a solution $\hat{\theta}$ that is consistent for the true parameter vector θ_0 .

See the Appendix for proof.

Theorem 2—Under conditions i. – iii. above, $\sqrt{N}(\hat{\theta} - \theta_0)$ is asymptotically normally distributed with mean zero and variance that can be consistently estimated by:

$$\left\{ \frac{1}{N} \sum_{i=1}^N U_i'(\theta) \right\}^{-1} \left\{ \frac{1}{N} \sum_{i=1}^N U_i(\hat{\theta}) U_i(\hat{\theta})^\top \right\} \left\{ \frac{1}{N} \sum_{i=1}^N U_i'(\hat{\theta}) \right\}^{-1}.$$

The proof of Theorem 2 is standard for estimating equations, using Taylor expansion and the central limit theorem, and can be found in for example, Yuan and Jennrich¹⁷.

Although the closed form of $U_i'(\theta)$ can be derived algebraically, in practice the computation is cumbersome and highly model dependent. To provide a general algorithm for fitting such models, we consider a numerical approximation using the last two iterations of $U_i'(\theta)$ at convergence. If k and $k+1$ are the last two iterations of the algorithm then the $(h, j)^{th}$ entry of $U_i'(\hat{\theta})$ is computed as the numerical partial derivative of the h -th component of U_i with respect to the j -th component of $\hat{\theta}$ using $\hat{\theta}^k$ and $\hat{\theta}^{k+1}$.

4 Simulation experiments

We carried out simulation experiments to evaluate the inference procedure described above, including the variance estimator. We also investigated the effect of misspecified error correlation structures, as well as non-normally distributed data. Although we do not make the assumption of normally distributed data, the formulas in (6) for the E-step were motivated by the multivariate normal distribution. In the following, we describe some representative results.

For each scenario presented below we simulated $N = 100$ individuals, each with two outcomes at five time points. Data were generated using fixed effect values as given in Tables 1–4, where β_{10} , β_{11} and β_{12} denote the fixed intercept and covariate effects for outcome 1, and similarly β_{20} , β_{21} and β_{22} for outcome 2. The first covariate in $x_{ijt} = x_{it}$ was distributed as $N(0, 2)$, and when there was a random slope in the model, it referred to the random effect on this first covariate; the second covariate was Bernoulli (0.3). The error standard deviations were σ_1 and σ_2 for outcomes 1 and 2, and R was their correlation. We considered either a random intercept or both a random intercept and random slope (that were correlated) in the model, with the random effects following normal distribution with mean zero and variance-covariance given in each table. In Table 1 and 2, D_1 and D_2 denote the variances of the single random effect for outcomes 1 and 2, respectively; in Table 3 and 4, D_{11} , D_{12} and ρ_1 denote the variances of the random intercept, the random slope, and their correlation for outcome 1, and similarly D_{21} , D_{22} and ρ_2 for outcome 2. A scenario with three outcomes and independent, exchangeable, and unstructured working correlations was also considered, and the results are included in the supplement materials. We ran 5,000 trials for each simulated scenario.

As mentioned earlier, we focus on examining the following two aspects:

- a. Correctly and incorrectly specified error correlations:

In all the tables shown data were generated using a correlated error structure. In the top half of each table model (1) was fitted using an independent working

correlation structure, while in the bottom half it was fitted using an exchangeable working correlation structure.

b. Normally and non-normally distributed errors:

In Table 1 and 3 the errors were normally distributed. In Table 2 and 4 the errors had either a 50:50 mixture of two normal distributions with means at -1 and 1 , or a Weibull distribution with a shape parameter of one and the scale parameter chosen so as to give the specified error variances.

In the tables we provide the average of the parameter estimates ('Estimate') over the 5000 simulated trials as well as the average of the standard errors ('SE') using the sandwich estimator as described in Section 3. We also give the sample standard deviation ('Sample SD') of the parameter estimates over the 5000 runs, which approximates the true standard deviation of the parameter estimates, and the empirical coverage probabilities ('Coverage') of the nominal 95% confidence intervals formed using SE and the asymptotic normality. Note that with 5000 runs the margin of error for the empirical coverage probabilities is 0.3%; that is we expect the empirical coverage to be mostly within 94.4%–95.6% if the true coverage is 95%.

From the tables we see that the estimates of the regression parameters were quite accurate, including the coverage of the confidence intervals, both under the misspecified error correlations and under non-normality. There was very little loss of efficiency in the estimation of the regression coefficients when the working correlation structure is misspecified. For comparison purposes we also provide the results using R package '*lme4*' to fit a separate linear mixed effects model to one outcome at a time in Tables 1 and 3, for normally distributed errors; separate modeling results corresponding to Tables 2 and 4 for non-normally distributed errors are provided in the Supplemental Materials. Note that the '*lme4*' package does not provide the SE's for the estimated variance components. The coverage probabilities of the estimated regression parameters were (very) slightly better in the separate analyses using '*lme4*', which is perhaps consistent with the known inefficiency of the sandwich variance estimator that we use¹⁸. We note that the sample SD's are very comparable between the joint modeling and the separate analyses for the regression parameters, and notably smaller under the joint models for some of the variance components under independent working correlation, which is further reduced under the exchangeable working correlation (see below).

The variance components were also accurately estimated under both the normal and the mixture of normals error distribution, but there was some bias and under-coverage of the confidence intervals for the error variances (as well as the correlation of the random intercept and slope) under the Weibull error distribution. There was some gain in efficiency in the estimation of the variance components when the working correlation structure was correctly specified. As R represents the parameters of a working correlation structure, like in the GEE software we do not estimate its variance.

The Supplemental Materials show that the estimates were generally well-approximated by the asymptotic normal distribution, and that the SE's for the variance parameters had some right skewness (this again relates to the performance of the sandwich variance estimator).

The Supplemental Materials also contain the simulation results for a larger sample size $N=1,000$, which are similar to the above.

5 Application: Nutrition Data

Here we apply our method to data from the Women's Healthy Eating and Living (WHEL) Study. The WHEL Study was a multi-site dietary intervention trial which assessed the impact of a low-fat, high-vegetable/fruit/fiber diet on preventing breast cancer recurrence³. Between 1995 and 2000, a total of 3088 women who had completed treatment for primary breast cancer were randomly assigned to one of two diet groups, stratified by stage of disease, age at diagnosis, and clinic site. The control group was advised to consume a diet consistent with National Cancer Institute dietary recommendations for cancer prevention, while an intensive telephone counseling approach was used to teach the intervention group to increase consumption of fruits and vegetables rich in micronutrients. Participants in the WHEL study ranged in age from 26 to 71 years at diagnosis, averaging 51 years. Approximately 40% of the WHEL sample was diagnosed with Stage I, 55% with Stage II, and 5% with Stage IIIA breast cancer. The ethnic distribution of WHEL women was 85% Caucasian-American, 5% Hispanic, 4% African-American, 4% Asian/Pacific Islander, with the remaining 2% comprised of other ethnicities. The study was completed in June 2006⁴.

The WHEL study has a rich database (<http://libraries.ucsd.edu/ssds/wheel.html>) of nutritional data collected longitudinally at study entry, and 1- and 4-years post randomization. The primary method for collecting information on participant dietary intake was the 24-hour recall. Repeat 24-hour recalls of dietary intake were collected during telephone interviews by trained dietary assessors blinded to the intervention or control group assignment of the participants. During these recalls participants were queried about their food intake during the previous 24-hours. Assessments at a particular time-point (study entry, year 1, or year 4) consisted of a set of four 24-hour dietary recalls collected over a three-week period, which included two weekdays and two weekend days. These four recalls were averaged, and this average constituted the 24-hour recall intake measure for that time-point. Nutrient calculations were performed using the Nutrition Data System for Research (NDS-R) software Food and Nutrient Database 31, version 4.03, released November 2000 by Nutrition Coordinating Center at University of Minnesota.

In applying our method, we consider the effect of the WHEL intervention over time on the following three outcomes: fat intake (g/day), fiber intake (g/day), and vegetable intake (servings/day) based on the 24-hour diet recalls. For illustration purposes we include in the analysis 2274 women with complete data on the three outcomes at all three time points. In Figure 1 the dashed lines represent the three outcomes of 30 randomly selected individuals from each of the randomized groups over time, and Table 5 displays their Pearson correlation matrices at the different times. It is clear that the three outcomes are correlated, as one might expect.

In carrying out the analysis to compare the phone counseling intervention with the active control group, we use the three outcomes at 1 and 4 years as dependent variables, time is treated as a continuous variable, with the baseline fat, fiber, and vegetable intakes, together

with baseline weight (kg), as covariates. We assume an unstructured working correlation R and a random slope over time. In Table 6 the intervention by phone counseling has helped to significantly (p -values < 0.001) reduce the fat intake, and increase the fiber and vegetable intakes, as compared to the active control group. The baseline intakes are significantly associated with the corresponding outcomes at the later time points. The results for fitting three separate models for the outcomes one at a time using *lme4* are very similar (provided in the Supplement Materials), but will not enable the testing we carry out below.

Under model (7) with w_{it} as the intervention variable, a Wald test for $H_0 : \alpha_1 = \alpha_2 = \alpha_3 = 0$ tests the effects of intervention across all three outcomes. This has an

$\chi^2_3 = (\hat{\alpha}_1, \hat{\alpha}_2, \hat{\alpha}_3) \text{Cov}(\hat{\alpha}_1, \hat{\alpha}_2, \hat{\alpha}_3)^{-1} (\hat{\alpha}_1, \hat{\alpha}_2, \hat{\alpha}_3)^T = 809.6$ (p -value < 0.001), indicating that healthy eating habits improved overall. The estimates in Table 6 also confirm the time trend as we observe in Figure 1: from 1 to 4 years there has been an increase in fat intake, and decreases in fiber and vegetable intakes; in other words, the intervention (including active controlling) effects seem to deteriorate over time in both groups, a feature that is common in many behavioral intervention studies whereby early successful changes are followed by some attenuation. This is also confirmed by a Wald test for time across all three outcomes ($\chi^2_3 = 498.5$, p -value < 0.001). In the Supplement Materials we also provide a model fit including an intervention by time interaction.

In testing whether the intervention has a common effect on all three outcomes as discussed in Section 2.3 ($H_0 : -\alpha_1 = \alpha_2 = \alpha_3$, since the effect on fat is in the opposite direction of the other two), we had an $\chi^2_2 = 46.8$ (p -value < 0.001) rejecting the null hypothesis of a common intervention effect after scaling. From Table 6 it appears that there might be a common (scaled) intervention effect for fiber and vegetable intakes, since the scaled estimates (i.e. the ratio of the estimated intervention effect and σ_j) for these two outcomes were 1.141 and 1.012, respectively. The Wald test for $H_0 : \alpha_2 = \alpha_3$, however, rejected the null of a common intervention effect ($\chi^2_1 = 8.400$, p -value = 0.004). If we nonetheless fit a common intervention effect for these two outcomes as an illustration, the estimated common scaled effect is 1.089 (SE = 0.042); together with the intervention effect on fat we had a $\chi^2_2 = 838.1$ (p -value < 0.001) for testing the zero intervention effect on all three outcomes under this submodel, as compared to $\chi^2_3 = 809.6$ above.

In Tables 7 and 8, we modeled the trajectory of the three outcomes from baseline to 1 year then 4 years within each study arm. In this case, time was modeled as a categorical variable with baseline as the intercept (i.e. reference group), so that the estimates for year 1 and 4 in the tables are the estimated changes from baseline to year 1 and from baseline to year 4, respectively. A random intercept is included for each outcome. The estimated mean trajectories are super-imposed in Figure 1 using the black solid lines. In the phone counseling group for all three outcomes the larger intervention effects as compared to baseline were seen at year 1, and they became attenuated at year 4 although remained significant when compared to the baseline intakes. For the active control group there was some intervention effect for fat at year 1, but by year 4 all three outcomes were worse when compared to the baseline, with fiber intake significantly so. At the suggestion of a reviewer

in the Supplement Materials we also provide a model fit including both groups and time as categorical; we note that due to randomization at baseline the distributions of the three outcomes are not expected to be different between the two groups, and this is indeed the case as reflected by the p -values for ‘intervention’.

We do not report p -values for the variance parameters as zero variance is on the boundary of the parameter space, and the sampling distributions of the test statistics are generally no longer asymptotically normal^{19–21}.

We note that there were 814 women with some missing outcomes that were not including in the analysis above. A test of the missing completely at random (MCAR) assumption²² shows that MCAR is rejected for fiber and vegetable intakes (data not shown). It is known that the GEE type approaches can lead to biased estimates under the missing at random (MAR) or missing not at random (MNAR) mechanisms; and we further discuss this missing data problem in the last section.

Finally we acknowledge (and discuss more below) that methods for model diagnostics and selection are to be developed under model (1). The structure of the WHEL data that we consider here is relatively simple, in that there are only three outcomes reflecting nutrition, and two time points after randomization. With the random effects capturing correlation among the outcomes longitudinally, the data may not support more complex modeling such as additionally correlated error terms over time. From Figure 1 we see that the variances of the outcomes do not appear to change drastically over time, although as we stated earlier this may not reflect directly whether the error variances change over time. Please see below for more discussion.

6 Extensions

There are various possible extensions to model (1).

1. Correlated errors—In the above we have assumed that $\text{Cor}(e_{ijt}, e_{iks}) = 0$ for any $t \neq s$, that is, the errors are uncorrelated over time. When this is no longer the case we may have $\text{Cor}(e_{ijt}, e_{ijs}) \neq 0$ for some $t \neq s$, or $\text{Cor}(e_{ijt}, e_{iks}) \neq 0$ for some $j \neq k$ and $t \neq s$. The ES motivated approach is to first augment the unobserved random effects. In this case we can expand the ‘cluster’ of correlated data from y_{it}^* to y_i^* , so that equation (3) becomes

$$\sum_{i=1}^N X_i^\top R_0^{-1} \left(y_i^* - X_i \tilde{\beta} - Z_i \tilde{b}_i \right) = 0, \quad (9)$$

where R_0 is a working correlation matrix for $\tilde{e}_i$.

As an example, for 3 outcomes with exchangeable correlation and 3 time points with AR(1) correlation, but $\text{Cor}(e_{ijt}, e_{iks}) = 0$ ($j \neq k$ and $t \neq s$),

$$R_0 = \begin{pmatrix} 1 & \rho & \rho & r_1 & & & r_1^2 \\ & 1 & \rho & r_2 & & & r_2^2 \\ & & 1 & r_3 & & & r_3^2 \\ & & & 1 & \rho & \rho & r_1 \\ & & & & 1 & \rho & r_2 \\ & & & & & 1 & r_3 \\ & & & & & & 1 \end{pmatrix}.$$

If in addition $\text{Cor}(e_{ijt}, e_{iks}) = 0$ for some $j \neq k$ and $t \neq s$, some of the zero entries in the matrix above will become non-zero. One possibility in the spirit of parsimony may be to use a large 9×9 exchangeable correlation matrix; but this of course assumes that all pairwise correlations, whether across time or across outcomes, are the same which may or may not be too strong. Other parametrizations are certainly possible depending on the application, and model selection can become an important aspect; see Discussion in the next section.

2. Heteroscedasticity over time—If the error variances change over time, commonly known as heteroscedasticity, while valid inference on the mean parameters under the linear models can typically be achieved as long as robust variance estimators are used²³, in our case we are interested in correctly estimating the error variances for scaling purposes. There are different ways to formulate the error variance as a function of time. In a balanced design where $n_i = T$, we can replace equation (4) with

$$\sum_{i=1}^N \left[\left\{ \frac{y_{ijt}}{\sigma_{jt}} \left(\frac{y_{ijt}}{\sigma_{jt}} - x_{ijt}^\top \tilde{\beta}_j - z_{ijt}^\top \tilde{b}_{ij} \right) - 1 \right\} \right]_{j=1, \dots, J; t=1, \dots, T} = 0. \quad (10)$$

One can also (choose to) model the error variance as a function of time. In some simple cases like $\sigma_j(t) = \sigma_j^2 t$ (say) then (4) can be replaced by

$$\sum_{i=1}^N \left[\sum_{t=1}^{n_i} \left\{ \frac{y_{ijt}}{\sigma_j^2 t} \left(\frac{y_{ijt}}{\sigma_j^2 t} - x_{ijt}^\top \tilde{\beta}_j - z_{ijt}^\top \tilde{b}_{ij} \right) - 1 \right\} \right]_{j=1, \dots, J} = 0. \quad (11)$$

But more generally in the literature variances have been modeled as functions of the mean^{24,25}, and different inference procedures should be developed which are beyond the scope of this paper.

3. Correlated random effects over different outcomes—In the above we have assumed that $\text{Cor}(b_{ij}, b_{ik}) = 0$ for any $j \neq k$, that is, the random effects are uncorrelated over different outcomes. However, if in applications need arises to allow the random effects for different outcomes to be correlated, we can modify equation (5) to be

$$\sum_{i=1}^N (\tilde{b}_i \tilde{b}_i^\top - \tilde{D}_0) = 0, \quad (12)$$

if $\tilde{D}_0 = \text{Cov}(\tilde{b})$ is unstructured. Similar equations can also be written out for different structures of $\tilde{D}_0$. Cnaan et al.¹⁴ discussed different ways of modeling correlation under the general linear mixed model, in particular modeling them through error correlations versus correlations induced by the random effects, and also warned against overparametrization. The modeling choice should depend on the application on hand, and we also discuss model selection in the next section.

Inference under these extensions can use the same approach as described in detail earlier. We note that the asymptotic scenario is for the number of subject $N \rightarrow \infty$. The computation of the sandwich variance estimator needs to be modified according to the specific algebra involved.

7 Discussion

In this paper we have proposed a general regression framework for multivariate longitudinal data which combines the commonly used marginal and conditional modeling, marginal across outcomes and conditional longitudinally. An inference procedure is developed using estimating equations together with the ES algorithm, which, under standard regularity conditions, provides a unique, consistent, and asymptotically normally distributed estimate of the parameters. Via simulation studies we have found the estimator to be robust against misspecified working error correlation structure in finite samples. The simulations have also shown that the E-step formulas that were motivated by multivariate normal distribution are robust for non-normally distributed errors, especially for inference on the regression parameters that are of interest. Through application to the WHEL nutrition intervention data we have illustrated the usefulness of the approach analyzing multiple outcomes simultaneously. In both simulations and WHEL data analysis we see that joint modeling gives regression results very similar to analyzing the outcomes separately; the latter, however, would not enable testing of an overall effect (either common after scaling or uncommon) on all outcomes, unless one adjusts for multiple testing and there is not a clear and efficient way to do so (Bonferroni type adjustments are typically conservative and inefficient).

As we noted earlier while the marginal approach and the conditional approach are both well-known in the correlated data literature, the combination of the two has not been widely used in practice. One such work somewhat closely related to ours in terms of algorithm is Rosen et al.²⁶, who extended the so-called mixture-of-experts models^{27,28} for i.i.d. data to correlated setting, using a GEE type approach. ‘Experts’ here came from terminology in the field of neural network, and refer to functions; these are a rich class of models, as the response of interest given the covariates follows a finite mixture distribution where the mixing probabilities depend on the covariates. Rosen et al.²⁶ extended the mixture-of-experts models to correlated response data that included longitudinal data, but they did not

consider multiple outcomes in addition to the longitudinal aspect. In particular, any correlation among the (longitudinal) data are handled using a marginal GEE approach, whereas their latent variables stemmed from the latent classes in the mixture distribution. For their purposes Rosen et al.²⁶ also proposed the ES algorithm, where the ‘S’ stood for ‘solution’ to the estimating equations; but otherwise theirs is the same algorithm as that of Elashoff and Ryan¹².

Our approach in studying the asymptotic properties of the estimator is broadly applicable and can be used both for estimating equations and for likelihood methods. We have explicitly expressed the conditional expectation of the complete data estimating equations at convergence of the ES algorithm, which is the actual estimating equation that defines the estimator. Although the well-known EM algorithm can be seen as a special case of the ES algorithm when applied to the likelihood score equation, we note that the asymptotic properties of the maximum likelihood estimator (MLE) are usually derived independent of the EM algorithm.

Missing data pose a major challenge in the analysis of longitudinal data. In the MCAR case most statistical approaches will give valid inference, including likelihood based methods and GEE. GEE, however, can give biased estimates under MAR when MCAR is violated^{29–31}, although the bias can be corrected by using inverse probability weighting (IPW) approaches³². As our combined marginal-conditional approach is an estimating equations type approach, the bias resulting from violation of MCAR assumption should also be corrected by using weights. How such a weighting approach can be developed together with the ES algorithm is the next project that we plan to work on.

As discussed in the previous section, different extensions to model (1) are possible, especially in the modeling of the variance components. Model selection tools will be useful for this purpose. Broadly speaking, hypothesis testing and information based criteria can both be used for model selection. Testing of variance components often needs to handle boundary parameter value problems^{20,21,33,34}. Akaike³⁵ type information criteria have been developed both for generalized estimating equations³⁶, and when the interest lies in the estimation of the random effects themselves^{37,38}. In addition model diagnostics is clearly important. With the presence of random effects residuals may not be as effective as in, for example, linear regression.³⁹ These will be topics of open research if the joint marginal-conditional model gains more use in practice.

An R package is currently under development that implements the approach developed in this paper. For future work it is also known that accurately modeling the error correlation structure can improve the estimation efficiency for the generalized estimating equations¹¹. It is likely that this is the case in the presence of the unobserved random effects as well. Improving efficiency is an open area of research for the future. In addition since the GEE approach can be applied to other types of outcomes such as binary or Poisson, we expect that the combined modeling and inference procedure can also be extended. The E-step, however, may be more complex computationally, and may not have closed form expressions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Rationale for equation (4)

Equation (4) is based on the fact that for any random variable Y (in this case y_{ijt}/σ_j) with $\text{Var}(Y) = 1$, we have

$$1 = \text{Var}(Y) = E\{Y - E(Y)\}^2 = E[Y\{Y - E(Y)\} - E(Y)\{Y - E(Y)\}] = E[Y\{Y - E(Y)\}]$$

because $E[E(Y)\{Y - E(Y)\}] = 0$.

The estimating equations (without conditional on the random effects)

At the convergence of the ES algorithm $\hat{\theta}$ solves the estimating equations $\sum_{i=1}^N U_i(\theta) = 0$, where

$$U_i(\theta) = \begin{cases} \sum_{t=1}^{n_i} X_{it}^\top R^{-1} \left[y_{it}^* - X_{it} \beta - Z_{it} \{ (\tilde{D} Z_i^\top)(Z_i \tilde{D} Z_i^\top + R^*)^{-1} (y_i^* - X_i \tilde{\beta}) \} \right] \\ \sum_{t=1}^{n_i} \left[\frac{y_{ijt}}{\sigma_j} \left\{ \frac{y_{ijt}}{\sigma_j} - x_{ijt}^\top \beta_j + z_{ijt}^\top [(\tilde{D} Z_i^\top)(Z_i \tilde{D} Z_i^\top + R^*)^{-1} (y_i^* - X_i \tilde{\beta})]_j \right\} - 1 \right], & \text{for } j=1, \dots, J \\ [\tilde{D} - (\tilde{D} Z_i^\top)(Z_i \tilde{D} Z_i^\top + R^*)^{-1} (\tilde{D} Z_i^\top)^\top + (\tilde{D} Z_i^\top)(Z_i \tilde{D} Z_i^\top + R^*)^{-1} (y_i^* - X_i \tilde{\beta})(y_i^* - X_i \tilde{\beta})^\top ((Z_i \tilde{D} Z_i^\top + R^*)^{-1})^\top (\tilde{D} Z_i^\top)^\top]_j - \hat{I} \end{cases}$$

Proof of Theorem 1

Proof—Under model (1) and conditional on the b_i 's, $\sum_{i=1}^N \mathcal{U}_i(\theta) = 0$ is a set of unbiased

estimating equations; that is $E\{\sum_{i=1}^N \mathcal{U}_i(\theta_0) | b_i\} = 0$. We then have

$E\{\sum_{i=1}^N U_i(\theta_0)\} = E\{\sum_{i=1}^N \mathcal{U}_i(\theta_0)\} = 0$. The rest of the proof follows immediately from Yuan and Jennrich¹⁷: basically the non-singularity of $E\{U'(\theta_0)\}$ in Assumption *iii*. ensures

that θ_0 is the unique zero of $E\{\sum_{i=1}^N U_i(\theta)\} = 0$ in a neighborhood of θ_0 ; the uniform

convergence in Assumption *ii*. together with the fact that $E\{\sum_{i=1}^N U_i(\theta_0)\} = 0$ establishes

that with probability one $\sum_{i=1}^N U_i(\theta) = 0$ has a solution $\hat{\theta}$ in any neighborhood of θ_0 for N sufficiently large; this in turn gives the consistency.

Figure 1.
Plot of 30 randomly selected individuals (dashed lines) over time; right: phone counseling group, left: control group. The black solid line is the fitted mean.

Table 1

Simulation results for two correlated outcomes, with a random intercept on each outcome. The errors were normally distributed.

Work Corr.	True	Joint Model				Separate Models			
		Estimate	SE	Sample SD	Coverage	Estimate	SE	Sample SD	Coverage
Ind.									
β_{10}	1	1.000	0.147	0.146	95.0%	1.002	0.147	0.146	95.0%
β_{11}	1	0.999	0.047	0.048	94.4%	1.000	0.047	0.048	94.8%
β_{12}	3	2.994	0.206	0.204	94.8%	2.998	0.207	0.204	95.3%
β_{20}	1.5	1.501	0.147	0.149	94.8%	1.503	0.148	0.149	95.1%
β_{21}	2	1.997	0.047	0.048	93.9%	2.000	0.048	0.048	94.4%
β_{22}	0.5	0.495	0.206	0.207	94.6%	0.496	0.207	0.208	95.1%
σ_1	2	1.994	0.070	0.072	93.7%	1.998	–	0.072	–
σ_2	2	1.994	0.070	0.070	93.9%	1.998	–	0.071	–
$\sqrt{D_1}$	1	0.978	0.129	0.132	94.1%	0.989	–	0.132	–
$\sqrt{D_2}$	1	0.980	0.129	0.135	93.9%	0.992	–	0.135	–
Exch.									
β_{10}	1	1.000	0.147	0.146	94.9%				
β_{11}	1	0.999	0.047	0.048	94.5%				
β_{12}	3	2.994	0.205	0.204	94.8%				
β_{20}	1.5	1.502	0.147	0.149	94.9%				
β_{21}	2	1.997	0.047	0.048	94.0%				
β_{22}	0.5	0.495	0.205	0.207	94.6%				
σ_1	2	1.992	0.070	0.072	93.7%				
σ_2	2	1.993	0.070	0.070	94.4%				
$\sqrt{D_1}$	1	0.981	0.126	0.129	94.0%				
$\sqrt{D_2}$	1	0.984	0.126	0.131	93.8%				

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Separate Models		Joint Model			
Work Corr.	True	Estimate	SE	Sample SD	Coverage
<i>R</i>	0.3	0.319	–	–	–

Table 2

Simulation results for two correlated outcomes, with a random intercept on each outcome. The errors were non-normally distributed.

Work Corr.	True	Mixture				Weibull			
		Estimate	SE	Sample SD	Coverage	Estimate	SE	Sample SD	Coverage
Ind.									
β_{10}	1	1.000	0.147	0.149	94.0%	0.997	0.147	0.146	94.6%
β_{11}	1	0.999	0.047	0.048	94.4%	0.989	0.050	0.049	95.2%
β_{12}	3	2.996	0.206	0.209	94.4%	2.968	0.210	0.208	94.1%
β_{20}	1.5	1.500	0.147	0.148	94.8%	1.496	0.149	0.145	94.9%
β_{21}	2	1.997	0.047	0.047	94.5%	1.980	0.056	0.049	96.8%
β_{22}	0.5	0.495	0.206	0.205	94.8%	0.491	0.205	0.204	94.3%
σ_1	2	1.995	0.068	0.070	94.1%	1.983	0.197	0.225	88.2%
σ_2	2	1.996	0.068	0.070	93.9%	1.987	0.198	0.224	88.4%
$\sqrt{D_1}$	1	0.978	0.129	0.133	93.9%	0.972	0.130	0.134	94.4%
$\sqrt{D_2}$	1	0.982	0.130	0.132	94.3%	0.974	0.130	0.134	95.0%
Exch.									
β_{10}	1	1.000	0.147	0.149	93.8%	0.997	0.147	0.146	94.6%
β_{11}	1	0.999	0.047	0.048	94.5%	0.989	0.049	0.048	95.2%
β_{12}	3	2.996	0.205	0.209	94.6%	2.968	0.210	0.208	94.4%
β_{20}	1.5	1.500	0.147	0.148	94.7%	1.496	0.149	0.145	94.9%
β_{21}	2	1.997	0.047	0.047	94.4%	1.980	0.056	0.049	96.8%
β_{22}	0.5	0.495	0.205	0.206	94.9%	0.491	0.205	0.204	94.1%
σ_1	2	1.993	0.069	0.069	94.1%	1.982	0.198	0.225	88.2%
σ_2	2	1.995	0.068	0.069	94.5%	1.986	0.198	0.224	88.4%
$\sqrt{D_1}$	1	0.982	0.126	0.129	94.1%	0.974	0.127	0.131	94.8%
$\sqrt{D_2}$	1	0.985	0.127	0.129	94.4%	0.976	0.127	0.131	95.0%

		Mixture				Weibull			
Work Corr.	True	Estimate	SE	Sample SD	Coverage	Estimate	SE	Sample SD	Coverage
R	0.3	0.319	-	-	-	0.313	-	-	-

Table 3

Simulation results for two correlated outcomes, with a random intercept and a random slope on each outcome. The errors were normally distributed.

Work Corr.	True	Joint Model			Separate Models				
		Estimate	SE	Sample SD	Coverage	Estimate	SE	Sample SD	Coverage
Ind.									
β_{10}	1	0.999	0.155	0.159	94.2%	1.001	0.155	0.159	94.3%
β_{11}	1	1.000	0.114	0.115	94.6%	1.001	0.114	0.115	94.6%
β_{12}	3	2.997	0.222	0.223	94.3%	3.002	0.223	0.224	94.7%
β_{20}	1.5	1.503	0.307	0.304	94.9%	1.505	0.307	0.305	94.7%
β_{21}	2	2.001	0.184	0.186	94.4%	2.004	0.184	0.186	94.4%
β_{22}	0.5	0.495	0.439	0.437	94.8%	0.497	0.441	0.438	95.0%
σ_1	2	1.994	0.079	0.079	94.4%	1.997	–	0.080	–
σ_2	4	3.989	0.157	0.159	93.9%	3.999	–	0.163	–
$\sqrt{D_{11}}$	1	0.979	0.142	0.146	94.3%	0.989	–	0.154	–
$\sqrt{D_{12}}$	1	0.989	0.090	0.091	93.5%	0.997	–	0.092	–
ρ_1	0.5	0.509	0.139	0.145	92.8%	0.505	–	0.147	–
$\sqrt{D_{21}}$	2	1.965	0.279	0.275	95.4%	1.967	–	0.345	–
$\sqrt{D_{22}}$	1.5	1.478	0.155	0.164	92.6%	1.492	–	0.165	–
ρ_2	0.5	0.511	0.148	0.156	92.1%	0.502	–	0.163	–
Exch.									
β_{10}	1.	0.999	0.154	0.158	94.4%				
β_{11}	1	0.999	0.114	0.114	94.6%				
β_{12}	3	2.996	0.221	0.222	94.3%				
β_{20}	1.5	1.503	0.306	0.304	94.9%				
β_{21}	2	2.001	0.183	0.185	94.5%				
β_{22}	0.5	0.496	0.437	0.434	94.8%				

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Work Corr.	True	Joint Model			Separate Models		
		Estimate	SE	Sample SD	Coverage	Estimate	SE
σ_1	2	1.983	0.081	0.079	94.5%		
σ_2	4	3.972	0.160	0.156	94.3%		
$\sqrt{D_{11}}$	1	0.998	0.130	0.134	94.5%		
$\sqrt{D_{12}}$	1	0.993	0.088	0.089	93.9%		
ρ_1	0.5	0.495	0.128	0.133	93.3%		
$\sqrt{D_{21}}$	2	1.997	0.258	0.258	95.3%		
$\sqrt{D_{22}}$	1.5	1.487	0.152	0.160	93.2%		
ρ_2	0.5	0.496	0.138	0.144	92.6%		
R	0.5	0.552	—	—	—		

Simulation results for two correlated outcomes, with a random intercept and a random slope on each outcome. The errors were non-normally distributed.

Table 4

Work Corr.	True	Mixture			Weibull				
		Estimate	SE	Sample SD	Coverage	Estimate	SE	Sample SD	Coverage
Ind.									
β_{10}	1	0.997	0.155	0.154	95.0%	0.998	0.155	0.154	94.8%
β_{11}	1	0.997	0.114	0.115	94.7%	0.994	0.116	0.114	95.0%
β_{12}	3	2.993	0.222	0.223	94.4%	2.967	0.226	0.227	94.4%
β_{20}	1.5	1.493	0.307	0.309	94.7%	1.479	0.308	0.315	94.0%
β_{21}	2	1.998	0.184	0.186	94.5%	1.959	0.201	0.221	95.8%
β_{22}	0.5	0.500	0.439	0.441	94.6%	0.473	0.435	0.641	93.8%
σ_1	2	1.996	0.077	0.079	94.2%	1.973	0.201	0.222	87.7%
σ_2	4	3.989	0.157	0.159	93.6%	3.863	0.546	0.660	82.0%
$\sqrt{D_{11}}$	1	0.982	0.142	0.143	94.7%	0.972	0.156	0.161	95.1%
$\sqrt{D_{12}}$	1	0.989	0.090	0.092	93.0%	0.979	0.098	0.100	92.6%
ρ_1	0.5	0.512	0.137	0.143	93.0%	0.507	0.165	0.174	92.7%
$\sqrt{D_{21}}$	2	1.962	0.286	0.282	95.1%	1.990	0.407	3.211	95.2%
$\sqrt{D_{22}}$	1.5	1.480	0.158	0.162	93.0%	1.469	0.215	0.442	92.8%
ρ_2	0.5	0.511	0.148	0.158	91.7%	0.506	0.191	0.233	89.5%
Exch.									
β_{10}	1	0.996	0.154	0.153	95.0%	0.998	0.154	0.154	94.7%
β_{11}	1	0.998	0.114	0.115	94.7%	0.994	0.115	0.114	95.1%
β_{12}	3	2.993	0.220	0.221	94.5%	2.965	0.225	0.226	94.2%
β_{20}	1.5	1.492	0.306	0.309	94.5%	1.480	0.307	0.308	94.1%
β_{21}	2	1.998	0.184	0.186	94.5%	1.956	0.198	0.187	95.9%
β_{22}	0.5	0.500	0.436	0.437	94.8%	0.482	0.424	0.447	94.1%

Work Corr.	True	Mixture				Weibull			
		Estimate	SE	Sample SD	Coverage	Estimate	SE	Sample SD	Coverage
σ_1	2	1.986	0.080	0.079	93.9%	1.963	0.202	0.219	87.7%
σ_2	4	3.972	0.159	0.159	93.7%	3.846	0.545	0.652	82.2%
$\sqrt{D_{11}}$	1	1.000	0.130	0.133	94.9%	0.987	0.143	0.150	95.0%
$\sqrt{D_{12}}$	1	0.994	0.088	0.090	93.1%	0.983	0.095	0.097	92.6%
ρ_1	0.5	0.496	0.127	0.132	93.4%	0.493	0.146	0.158	93.3%
$\sqrt{D_{21}}$	2	1.995	0.258	0.263	94.9%	1.972	0.314	0.585	95.4%
$\sqrt{D_{22}}$	1.5	1.487	0.152	0.159	93.0%	1.469	0.195	0.226	93.6%
ρ_2	0.5	0.497	0.138	0.145	92.5%	0.495	0.183	0.212	90.9%
R	0.5	0.553	—	—	—	0.510	—	—	—

Table 5

Correlation among the three outcomes over time.

Baseline			Year 1			Year 4		
Fat	Fiber	Veg.	Fat	Fiber	Veg.	Fat	Fiber	Veg.
Fat	1		1			1		
Fiber	-0.014	1	-0.181	1		-0.086	1	
Veg.	-0.090	0.590	-0.235	0.674	1	-0.122	0.648	1

Table 6

Comparison of two intervention groups while adjusting for baseline covariates.

	Fat			Fiber			Veg.																		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value																
Intercept	28.100	1.854	<0.001	14.351	0.801	<0.001	1.827	0.175	<0.001																
Weight0	0.005	0.021	0.789	-0.035	0.008	<0.001	-0.003	0.002	0.089																
Fat0	0.386	0.017	<0.001	-0.036	0.006	<0.001	-0.007	0.001	<0.001																
Fib0	0.094	0.047	0.044	0.483	0.025	<0.001	0.034	0.005	<0.001																
Veg0	-0.172	0.242	0.478	0.526	0.104	<0.001	0.392	0.025	<0.001																
Time	5.213	0.417	<0.001	-2.859	0.156	<0.001	-0.249	0.038	<0.001																
Intervention	-9.818	0.622	<0.001	6.976	0.275	<0.001	1.489	0.059	<0.001																
σ	14.121	0.298	-	6.113	0.121	-	1.472	0.030	-																
$\sqrt{D}$	10.956	0.502	-	4.055	0.143	-	0.748	0.039	-																
R	<table><tr><td></td><td>Fat</td><td>Fiber</td><td>Veg.</td></tr><tr><td>Fat</td><td>1</td><td></td><td></td></tr><tr><td>Fiber</td><td>-0.013</td><td>1</td><td></td></tr><tr><td>Veg.</td><td>-0.063</td><td>0.678</td><td>1</td></tr></table>										Fat	Fiber	Veg.	Fat	1			Fiber	-0.013	1		Veg.	-0.063	0.678	1
	Fat	Fiber	Veg.																						
Fat	1																								
Fiber	-0.013	1																							
Veg.	-0.063	0.678	1																						

Table 7

Time trajectory from baseline to 1 and 4 years (phone counseling group).

	Fat			Fiber			Veg.		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
Intercept	55.654	0.648	<0.001	21.545	0.259	<0.001	2.994	0.052	<0.001
Year 1	-14.463	0.656	<0.001	7.760	0.295	<0.001	1.720	0.061	<0.001
Year 4	-8.265	0.683	<0.001	3.866	0.281	<0.001	1.282	0.062	<0.001
σ	14.908	0.300	-	7.720	0.176	-	1.686	0.036	-
$\sqrt{D}$	12.046	0.495	-	4.895	0.216	-	0.936	0.052	-
R	Fat			Fiber			Veg.		
	1			1			1		
	Fiber			-0.067			1		
	Veg.			-0.108			0.674		

Table 8

Time trajectory from baseline to 1 and 4 years (active control group).

	Fat			Fiber			Veg.		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
Intercept	56.496	0.636	<0.001	21.377	0.233	<0.001	2.944	0.050	<0.001
Year 1	-4.230	0.629	<0.001	-0.193	0.208	0.354	0.067	0.049	0.174
Year 4	0.077	0.672	0.909	-2.099	0.211	<0.001	-0.007	0.053	0.896
σ	15.579	0.401	-	5.632	0.134	-	1.342	0.033	-
$\sqrt{D}$	14.707	0.531	-	5.285	0.187	-	0.980	0.041	-
R	Fat			Fiber			Veg.		
	1			1			1		
	Fiber			0.080			1		
	Veg.			-0.011			0.487		