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Improving Power in Small-Sample Longitudinal Studies when using Generalized Estimating Equations

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Summary

Generalized estimating equations (GEE) are often used for the marginal analysis of longitudinal data. Although much work has been done to improve the validity of GEE for the analysis of data arising from small-sample studies, little attention has been given to power in such settings. Therefore, we propose a valid GEE approach to improve power in small-sample longitudinal study settings in which the temporal spacing of outcomes is the same for each subject. Specifically, we use a modified empirical sandwich covariance matrix estimator within correlation structure selection criteria and test statistics. Use of this estimator can improve the accuracy of selection criteria and increase the degrees of freedom to be used for inference. The resulting impacts on power are demonstrated via a simulation study and application example.

Keywords

correlation selection; degrees of freedom; efficiency; empirical covariance matrix

1 Introduction

Generalized estimating equations (GEE) [1] are popular for the marginal analysis of correlated data. For instance, in longitudinal studies, N independent subjects are followed over time, and outcomes from the same subject are assumed to be correlated. In some practical settings, the number of subjects may be small. In such settings, statistical power can be low. Therefore, our interest is in improving power while maintaining the validity of inference in longitudinal study settings involving a small number of subjects.

An empirical sandwich estimator of the covariance matrix of regression parameter estimates resulting from the use of GEE is routinely used in practice because it is robust to misspecification of the working correlation structure [1]. Therefore, when N is large, valid inference can typically be attained. However, this empirical covariance estimator may result in invalid inference in small-sample settings because it can be both negatively biased and highly variable. Therefore, multiple corrections have been proposed to improve upon this estimator [2] and reduce its bias [3, 4, 5, 6, 7, 8, 9, 10, 11]. Furthermore, the use of critical values from a t-distribution or F-distribution, rather than from a standard normal or chi-

square distribution, respectively, has been proposed due to the variability in this covariance estimator [12, 4].

It is well-known that accurate modeling of the working correlation structure for use with GEE can improve estimation efficiency [13, 14, 15], and therefore power. Multiple selection criteria have therefore been proposed. For instance, see Westgate [16], who compared the performances of many criteria and found that criteria such as the ‘correlation information criterion’ (CIC) [17] and the ‘trace of the empirical covariance matrix’ (TECM) [16] criterion can work well. Furthermore, especially in small-sample settings, these criteria should account for, or penalize, the inflation of the covariance matrix of the regression parameter estimates due to the estimation of nuisance correlation parameters [10, 16, 11].

For small-sample longitudinal study settings in which the temporal spacing of outcomes is the same for each subject, we propose improving power via the use of a modified empirical sandwich covariance matrix estimator within correlation structure selection criteria and test statistics. This estimator combines previously cited approaches in order to attain valid inference and to more precisely estimate the true covariance matrix of the regression parameter estimates. Due to this enhanced precision, use of the modified estimator within correlation selection criteria such as the CIC or TECM can improve their selection accuracies, potentially reducing the variances of regression parameter estimates. Furthermore, when used within test statistics, the enhanced precision can result in an increase in degrees of freedom, which we will propose how to calculate. As a result of both of these impacts, power can increase.

In Section 2, we summarize GEE, review relevant methods for attaining valid small-sample inference, and discuss correlation selection criteria. Our proposed approach is then described in Section 3, and its impact on power is demonstrated via a simulation study and in an application example in Sections 4 and 5, respectively. Concluding remarks are given in Section 6.

2 GEE, Small-Sample Inference, and Correlation Selection

2.1 Generalized Estimating Equations

Suppose N subjects each contribute up to n observations having the same temporal spacing. For simplicity of presentation we assume there are no missing data. Denote the outcome vector for the i th subject by $\mathbf{Y}_i = [Y_{i1}, \dots, Y_{in}]^T$. To obtain a consistent estimate, $\hat{\boldsymbol{\beta}}$, of the regression parameters, $\boldsymbol{\beta} = [\beta_0, \beta_1, \dots, \beta_{p-1}]^T$, we set the GEE equal to 0 and solve

$\sum_{i=1}^N \mathbf{D}_i^T \mathbf{V}_i^{-1} (\mathbf{Y}_i - \boldsymbol{\mu}_i) = 0$ [1]. Here, $\boldsymbol{\mu}_i = E(\mathbf{Y}_i)$ using a link function f such that

$f(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta}$ for covariate values $\mathbf{x}_{ij} = [1, x_{1ij}, \dots, x_{(p-1)ij}]^T$, $\mathbf{D}_i = \boldsymbol{\mu}_i' \boldsymbol{\beta}^T$, and

$\mathbf{V}_i = \phi \mathbf{A}_i^{1/2} \mathbf{R}_i(\boldsymbol{\alpha}) \mathbf{A}_i^{1/2}$, $i = 1, \dots, N$. For subject i , $\phi \mathbf{A}_i$ is a diagonal matrix of working marginal variances, and $\mathbf{R}_i(\boldsymbol{\alpha})$ is the working correlation matrix with correlation parameter(s) given by $\boldsymbol{\alpha}$.

With respect to inference, $\hat{\boldsymbol{\beta}}$ is asymptotically normally distributed under mild regularity conditions [1]. Furthermore, assuming $\boldsymbol{\alpha}$ is known,

$$\text{Cov}(\hat{\beta}) \approx \sum_M \left(\sum_{i=1}^N \mathbf{D}_i^T \mathbf{V}_i^{-1} \text{Cov}(\mathbf{Y}_i) \mathbf{V}_i^{-1} \mathbf{D}_i \right) \sum_M, \quad (1)$$

where $\sum_M = \left(\sum_{i=1}^N \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i \right)^{-1}$. The empirical covariance estimator of Liang and Zeger [1],

$$\sum_{LZ} = \sum_M \left(\sum_{i=1}^N \mathbf{D}_i^T \mathbf{V}_i^{-1} \widehat{\text{Cov}}_{LZ}(\mathbf{Y}_i) \mathbf{V}_i^{-1} \mathbf{D}_i \right) \sum_M,$$

is routinely used in practice because it does not require the working structure to be correctly specified. Here, $\widehat{\text{Cov}}_{LZ}(\mathbf{Y}_i) = (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T$. In large-sample settings, use of $\widehat{\text{Cov}}_{LZ}(\hat{\beta})$ and critical values from either a standard normal or chi-square distribution will often yield valid inference. However, we do note that the working correlation matrix is within $\hat{\Sigma}_{LZ}$. Because the working correlation matrix may not be consistently estimated if it is not the true structure, $\hat{\Sigma}_{LZ}$ may not be consistent [18, 19].

2.2 Improvements to the Small-Sample Validity of Inference

Both the small-sample estimation variability of and bias in $\hat{\Sigma}_{LZ}$ can cause liberal inference. The smaller N is, the greater the estimation variability and bias. Specifically, because $\hat{\Sigma}_{LZ}$ incorporates empirical covariances from each subject, the estimation variability within $\hat{\Sigma}_{LZ}$ increases as N decreases. Therefore, critical values from a standard normal or chi-square distribution can be liberal [12]. The negative bias in $\hat{\Sigma}_{LZ}$ with respect to estimating $\text{Cov}(\hat{\beta})$ can come from two distinct sources. First, because parameters must be estimated, $\hat{\Sigma}_{LZ}$ actually incorporates $(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T$, rather than $(\mathbf{Y}_i - \boldsymbol{\mu}_i)(\mathbf{Y}_i - \boldsymbol{\mu}_i)^T$, $i = 1, \dots, N$. As the residual vectors tend to be smaller than the corresponding error vectors, $\hat{\Sigma}_{LZ}$ can be biased for the approximation given in Equation (1), with increasing bias as N decreases [4]. Second, the covariance approximation in Equation (1) assumes that either the correlation parameters are known or the correlation parameters have no influence on the estimation of β . In practice correlation parameters must be estimated. Therefore, when the working correlation structure involves one or more parameters to estimate, and these parameters influence the estimation of β , the estimation variability of GEE increases, therefore inflating $\text{Cov}(\hat{\beta})$ and creating even more bias in $\hat{\Sigma}_{LZ}$ [10, 11].

To address the estimation variability of $\hat{\Sigma}_{LZ}$, Pan and Wall [12] proposed a method for approximating degrees of freedom (df) to use with t- or F-tests, rather than z- or Wald chi-square tests. In short, df are obtained by estimating the variability of $\hat{\Sigma}_{LZ}$. Details are given in Supporting Material. To reduce the variability of $\hat{\Sigma}_{LZ}$ in balanced studies, Pan [2] proposed replacing $(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T$, $i = 1, \dots, N$, within $\hat{\Sigma}_{LZ}$ with

$$\widehat{\text{Cov}}_P(\mathbf{Y}_i) = \phi \mathbf{A}_i^{1/2} \mathbf{R}_U \mathbf{A}_i^{1/2} = \mathbf{A}_i^{1/2} \left(\frac{1}{N} \sum_{j=1}^N \mathbf{A}_j^{-1/2} (\mathbf{Y}_j - \hat{\boldsymbol{\mu}}_j) (\mathbf{Y}_j - \hat{\boldsymbol{\mu}}_j)^T \mathbf{A}_j^{-1/2} \right) \mathbf{A}_i^{1/2}.$$

We note that this approach assumes the marginal variances of the outcomes are modeled correctly, and there is a common correlation structure for each subject. Furthermore, even if there is not a common correlation structure across all subjects, there may be a common structure within certain groups of subjects, in which case $\widehat{\text{Cov}}_P(\mathbf{Y}_i)$ can be modified accordingly.

To reduce the first source of bias in $\hat{\Sigma}_{LZ}$ with respect to the approximation given in Equation (1), numerous approaches have been proposed [3, 4, 5, 6, 7, 8, 9]. For instance, Mancl and DeRouen [4] showed that

$E[(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T] \approx (\mathbf{I}_n - \mathbf{H}_i) \text{Cov}(\mathbf{Y}_i) (\mathbf{I}_n - \mathbf{H}_i^T)$, and Kauermann and Carroll [3] showed that $E[(\mathbf{Y}_i - \boldsymbol{\mu}_i)(\mathbf{Y}_i - \boldsymbol{\mu}_i)^T] = \text{Cov}(\mathbf{Y}_i) - \mathbf{H}_i \text{Cov}(\mathbf{Y}_i) [1 + O(n^{-1})]$ when the working covariance structure is correctly specified, implying that $E[(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T] \approx (\mathbf{I}_n - \mathbf{H}_i) \text{Cov}(\mathbf{Y}_i)$. Therefore, the corresponding bias-corrections estimate $\text{Cov}(\mathbf{Y}_i)$ with

$(\mathbf{I}_n - \mathbf{H}_i)^{-1} (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i) (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T (\mathbf{I}_n - \mathbf{H}_i^T)^{-1}$ and $(\mathbf{I}_n - \mathbf{H}_i)^{-1} (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i) (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T$, respectively, inside Equation (1). We note that $\mathbf{H}_i = \mathbf{D}_i \sum_M \mathbf{D}_i^T \mathbf{V}_i^{-1}$. Also, Kauermann and Carroll [3] were interested in corrected residual vectors, which results in the well-known version of their correction given by $(\mathbf{I}_n - \mathbf{H}_i)^{-1/2} (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i) (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T (\mathbf{I}_n - \mathbf{H}_i^T)^{-1/2}$.

Recently, Westgate [10, 11] showed that due to the estimation of correlation parameters, Equation (1) is incorrect because the covariance matrix can inflate. Specifically,

$$\text{Cov}(\hat{\boldsymbol{\beta}}) \approx (\mathbf{I}_p + \mathbf{G}) \sum_M \left(\sum_{i=1}^N \mathbf{D}_i^T \mathbf{V}_i^{-1} \text{Cov}(\mathbf{Y}_i) \mathbf{V}_i^{-1} \mathbf{D}_i \right) \sum_M (\mathbf{I}_p + \mathbf{G})^T,$$

where $\mathbf{I}_p$ is a $p \times p$ identity matrix and $\mathbf{G} = (\mathbf{G}_0, \mathbf{G}_1, \dots, \mathbf{G}_{p-1})$,

$$\mathbf{G}_r = - \sum_M \sum_{i=1}^N \mathbf{D}_i^T \mathbf{A}_i^{-1/2} \mathbf{R}_i^{-1} \frac{\partial \mathbf{R}_i(\hat{\boldsymbol{\alpha}}(\boldsymbol{\beta}))}{\partial \beta_r} \mathbf{R}_i^{-1} \mathbf{A}_i^{-1/2} (\mathbf{Y}_i - \boldsymbol{\mu}_i(\boldsymbol{\beta})).$$

Therefore, to reduce the second source of bias in $\hat{\Sigma}_{LZ}$ with respect to estimating $\text{Cov}(\hat{\boldsymbol{\beta}})$, this covariance inflation formula should be utilized. In practice, unknown parameters must be replaced with their corresponding estimates in $\mathbf{G}$. The resulting estimator accounting for both sources of bias is given by

$$\hat{\Sigma}_{CLZ} = (\mathbf{I}_p + \hat{\mathbf{G}}) \sum_M \left(\sum_{i=1}^N \mathbf{D}_i^T \mathbf{V}_i^{-1} \widetilde{\text{Cov}}(\mathbf{Y}_i) \mathbf{V}_i^{-1} \mathbf{D}_i \right) \sum_M (\mathbf{I}_p + \hat{\mathbf{G}})^T \quad (2)$$

Here, $\widetilde{\text{Cov}}(\mathbf{Y}_i) = (\mathbf{I}_n - \mathbf{H}_i)^{-c} (\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)(\mathbf{Y}_i - \hat{\boldsymbol{\mu}}_i)^T (\mathbf{I}_n - \mathbf{H}_i^T)^{-d}$, where

$\mathbf{H}_i = \mathbf{D}_i (\mathbf{I}_p + \hat{\mathbf{G}}) \sum_M \mathbf{D}_i^T \mathbf{V}_i^{-1}$ and c and d are constants with numerical values depending upon which bias correction is used.

We note that another small-sample bias-correction was proposed by Wang and Long [8], who simply modified $\mathbf{R}_U$ within $\widehat{\text{Cov}}_p(\mathbf{Y}_i)$ by incorporating the Mancl and DeRouen [4] correction, such that

$$\mathbf{R}_U = \left(\frac{1}{N} \sum_{j=1}^N \mathbf{A}_j^{-1/2} (\mathbf{I}_n - \mathbf{H}_j)^{-1} (\mathbf{Y}_j - \hat{\boldsymbol{\mu}}_j)(\mathbf{Y}_j - \hat{\boldsymbol{\mu}}_j)^T (\mathbf{I}_n - \mathbf{H}_j^T)^{-1} \mathbf{A}_j^{-1/2} \right).$$

We denote the resulting estimator by $\hat{\Sigma}_{WL}$. Furthermore, they extended the df approximation approach of Pan and Wall [12] for use with $\hat{\Sigma}_{WL}$. However, we found that their approximation can result in liberal inference; more detail is given in Supporting Material.

2.3 Correlation Selection

Although multiple correlation selection criteria have been proposed, two criteria that may be preferred are the CIC [17] and TECM [16]. These criteria have been shown to work well and, especially in the case of the TECM, are simple to obtain and explain to investigators [16]. In order to account for, or penalize, the estimation of nuisance correlation parameters, Westgate [16, 11] suggested the use of the covariance inflation formula within these criteria, rather than just the use of $\hat{\Sigma}_{LZ}$ which has historically been done. Therefore, the CIC and TECM select the working correlation structure that yields the smallest value for

$\text{tr}(\sum_I^{-1} \sum_{CLZ})$ or $\text{tr}(\hat{\Sigma}_{CLZ})$, respectively, where $\sum_I = (\sum_{i=1}^N \mathbf{D}_i^T \mathbf{A}_i^{-1} \mathbf{D}_i)^{-1}$. Furthermore, Westgate [11] demonstrated that the type of correction, for instance the Kauermann and Carroll [3] or Mancl and DeRouen [4] correction, for the first source of bias within $\hat{\Sigma}_{LZ}$ has negligible impact on correlation selection.

3 Proposed Approach

If we were only interested in maintaining the validity of inference, the estimator $\hat{\Sigma}_{CLZ}$ given in Equation (2) can be utilized [10, 11] with df obtained using the Pan and Wall [12] approach or by simply using $N - p$ df [4, 10, 11]. However, our goal is to improve power while maintaining the validity of inference. Our key to increase power is to improve upon the precision of $\hat{\Sigma}_{CLZ}$ as an estimator for $\text{Cov}(\boldsymbol{\beta})$ by utilizing the approach of Pan [2]. To maintain the validity of inference, the bias-corrections within $\hat{\Sigma}_{CLZ}$ are still used. As a result, our proposed covariance matrix estimator is given by

$$\hat{\Sigma}_{WB} = (I_p + \hat{G}) \sum_M \left(\sum_{i=1}^N D_i^T V_i^{-1} \widehat{\text{Cov}}_{WB}(Y_i) V_i^{-1} D_i \right) \sum_M (I_p + \hat{G})^T, \quad (3)$$

where

$$\widehat{\text{Cov}}_{WB}(Y_i) = \phi A_i^{1/2} \tilde{R}_U A_i^{1/2} = A_i^{1/2} \left(\frac{1}{N} \sum_{j=1}^N A_j^{-1/2} (I_n - H_j)^{-c} (Y_j - \hat{\mu}_j)(Y_j - \hat{\mu}_j)^T (I_n - H_j^T)^{-d} A_j^{-1/2} \right) A_i^{1/2}. \quad (4)$$

We note that $\hat{\Sigma}_{WB}$ has similarities with $\hat{\Sigma}_{WL}$. Therefore, besides just comparing df approximation methods in Supporting Material, we also discuss important differences between these two estimators.

Our approach to improving power in this manuscript is based on the use of $\tilde{R}_U$ as given in Equation (4), within Equation (3). Specifically, this usage can increase our precision for estimating $\text{Cov}(\hat{\beta})$, which will allow us to increase power using two distinct approaches. First, the df calculated using the approach of Pan and Wall [12] account for the variability of $\hat{\Sigma}_{LZ}$ or $\hat{\Sigma}_{CLZ}$. Therefore, since $\hat{\Sigma}_{WB}$ can estimate $\text{Cov}(\hat{\beta})$ more precisely, we can have an increase in df and thus power. For space considerations, formulas for calculating df, as well as derivations of these formulas, are given in Supporting Material. Second, by increasing precision for estimating $\text{Cov}(\hat{\beta})$, use of $\hat{\Sigma}_{WB}$ rather than $\hat{\Sigma}_{CLZ}$ within the CIC and TECM can improve the precision of these criteria and thus their selection accuracies, potentially reducing the variances of regression parameter estimates and thus increasing power. We note

that our proposed versions of the CIC and TECM are therefore given by $\text{tr}(\sum_I^{-1} \sum_{WB})$ and $\text{tr}(\hat{\Sigma}_{WB})$, respectively. We also point out that besides its utility in terms of attaining valid inference, use of the covariance inflation formula within $\hat{\Sigma}_{WB}$ can be important for our method because, as described by Westgate [16, 11], utilizing this formula within $\hat{\Sigma}_{CLZ}$ when used by correlation selection criteria can improve selection accuracy, therefore enhancing regression parameter estimation and thus power.

4 Simulation Study

4.1 Study Description

We now demonstrate our proposed method's potential to improve power via a simulation study. Specifically, the use of $\hat{\Sigma}_{WB}$, which assumes a common structure, within correlation selection criteria and Wald statistics with corresponding df obtained as given in Supporting Material will be compared with the use of $\hat{\Sigma}_{CLZ}$, which does not assume a common structure, within correlation selection criteria and Wald statistics with corresponding df obtained using the approach of Pan and Wall [12] or $N - p$ df. To our knowledge, there is

little information in the literature as to which type of df is preferred, Pan and Wall [12] or $N - p$ df, and therefore results are presented for both. Furthermore, of the corrections to the meat of the empirical covariance matrix estimator, the Mancl and DeRouen [4] and Kauermann and Carroll [3] corrections appear, to our knowledge, to be the most popular. These corrections have been studied in many manuscripts, and have been compared as well. For instance, Lu et al. [20] and Westgate [21, 11] have found the Mancl and DeRouen [4] approach to over-correct bias in some instances, whereas the simulation study of Westgate [10] found the Mancl and DeRouen [4] correction to work quite well. Therefore, our study will add to the literature on comparative performances of these corrections by presenting results from the use of both corrections. Furthermore, our study will show the differences in impact these two corrections have when used within our proposed estimator, $\hat{\Sigma}_{WB}$, and how this influences inference.

Simulation scenario 1 is based on the studies of Hin et al. [22], Hin and Wang [17], and Westgate [16, 11], and utilizes time-dependent covariates with values that vary across subjects. Specifically, we generate multivariate normal outcomes from the marginal mean structure given by $\mu_{ij} = \beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2ij}$, $j = 1, 2, 3, 4$; $i = 1, \dots, N$, where $\beta = [0, 0.3, 1.0]^T$, $\text{Var}(\varepsilon_{ij}) = 1$, and x_{1ij} and x_{2ij} , $j = 1, 2, 3, 4$; $i = 1, \dots, N$, were independently generated from $\text{Uniform}(0, 1)$. The number of subjects is either 10, 20, or 100.

Simulation scenario 2 uses covariates that represent time and a baseline variable that varies in value across subjects, similar in nature to covariates later utilized in our application example. Specifically, we generate multivariate normal outcomes from the marginal mean structure given by $\mu_{ij} = \beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2ij}$, $j = 1, 2, 3, 4$; $i = 1, \dots, N$, where $\beta = [50, 2, 0.5]^T$, $\text{Var}(\varepsilon_{ij}) = 100$, $x_{1j} = j - 1$, and x_{2j} was uniformly generated from the integers ranging from -15 to 15. Because our application example is based on 25 subjects, the number of subjects in this simulation scenario was chosen to be either 25 or 100.

For both scenarios, we present results from settings in which the true correlation structure is AR-1 with parameter values of either 0.3 or 0.7. In Supporting Material, we present results from a simulation study in which outcomes are binary, but only using a correlation value of 0.3 due to correlation constraints on binary outcomes [23, 24]. Results for each setting are based on 1,000 replications.

Tables 1 (Scenario 1) and 2 (Scenario 2) present empirical powers based on Wald tests using SEs obtained from $\hat{\Sigma}_{CLZ}$ and $\hat{\Sigma}_{WB}$. These tables' primary purpose is to demonstrate power increases resulting from the use of our proposed approach due to an increase in df. Therefore, empirical mean df are also presented. Results from the use of each of these two covariance estimators are given twice, once from the incorporation of the Mancl and DeRouen [4] correction and once from utilizing the Kauermann and Carroll [3] correction, in order to determine the influences of these corrections. Tests utilizing SEs from $\hat{\Sigma}_{CLZ}$ use either $N - p$ df or the Pan and Wall (PW) [12] method to estimate df, whereas tests incorporating SEs from $\hat{\Sigma}_{WB}$ utilize our proposed df (WB). Results from two-sided tests with null hypotheses of $H_0 : \beta_1 = 0$ and $H_0 : \beta_2 = 0$ are given separately to demonstrate scenarios with different degrees of power. All tests utilize a 0.05 significance level. For simplicity, results are from the use of a working AR-1 structure.

Table 3 presents results from the use of the TECM, incorporating either $\hat{\Sigma}_{CLZ}$ or $\hat{\Sigma}_{WB}$, to select either a working independence, exchangeable, or AR-1 structure in the settings of Scenario 1. We note that results from the use of the CIC were similar and are therefore not presented. First, empirical frequencies of selecting each structure are given. As accurate correlation selection can improve estimation precision, resulting empirical standard deviations (ESDs) of $\hat{\beta}_1$ and $\hat{\beta}_2$ are then given. Finally, empirical powers from tests resulting from the use of correlation selection and the given covariance estimator and df approach are presented, giving a reflection of the overall impact our proposed approach has on power. To shorten our presentation, we do not give empirical powers based on $N - p$ df, which tend to be equal to or smaller than empirical powers based on the Pan and Wall [12] df in this scenario. Furthermore, for space considerations results are not presented for Scenario 2 because correlation selection frequencies were not influenced by the type of covariance estimator in this scenario.

Additional tables are given in Supporting Material in order to present corresponding results that are useful for explaining our primary results presented below in Tables 1-3. Specifically, we give further detailed comparisons between the use of the Mancl and DeRouen [4] and Kauermann and Carroll [3] corrections. Furthermore, we demonstrate the validity of inference from our utilized methods and demonstrate the accuracy of $\hat{\Sigma}_{WB}$ relative to $\hat{\Sigma}_{CLZ}$.

We note that although not observed in Westgate [16], when N is very small, i.e. 10 or 20 in the settings of Scenario 1, selecting among competing working correlation structures can result in negatively biased standard error (SE) estimates (see Supporting Material), and therefore liberal inference. The reason for this is because selection criteria tend to choose the structure that essentially has been estimated to result in the smallest SEs. As this is not an issue if we only consider one working structure, we used a penalty such that for every additional structure under consideration we remove one degree of freedom for hypothesis testing. For instance, in our study, we used a two degree of freedom penalty. We found this to work well, with a few exceptions for small N , as explained in Supporting Material. We note that with our proposed df, this df penalty can have negligible impact, and was devised for use with the other methods having fewer df.

4.2 Description of Results

4.2.1 Power Due to Degrees of Freedom—Table 1 shows that overall in Scenario 1, use of our proposed covariance estimator, $\hat{\Sigma}_{WB}$, and df improved empirical power relative to the use of $\hat{\Sigma}_{CLZ}$ and either the Pan and Wall [12] or $N - p$ df. Although empirical powers were similar in many settings in which β_1 was of interest or $N = 100$, the proposed approach notably increased power for tests based on β_2 and when $N = 10$ or 20. The reason for this increase in power is due to the increased precision in $\hat{\Sigma}_{WB}$ relative to $\hat{\Sigma}_{CLZ}$, and therefore the increase in df. For instance, in the setting in which $N = 10$ and $\rho = 0.7$, use of $\hat{\Sigma}_{WB}$ with our df had 0.07 and 0.10 greater power than the use of $\hat{\Sigma}_{CLZ}$ with either the Pan and Wall [12] or $N - p$ df, respectively, when utilizing the Kauermann and Carroll [3] correction. When incorporating the Mancl and DeRouen [4] correction in this setting, the power gains via use of our method were 0.12 and 0.16, respectively.

With respect to Scenario 2, Table 2 shows that regardless of the covariance estimator and type of df, empirical powers were similar corresponding to the test for β_1 , the adjusted mean impact of time. Furthermore, the empirical means of our proposed df and the Pan and Wall [12] df were equivalent (see Section 1.4 in Supporting Materials for an explanation). Alternatively, when conducting tests with respect to β_2 , our proposed df were notably larger on average than the Pan and Wall [12] df and therefore resulted in notably larger power when $N = 25$. We also note that $N - p$ df worked almost as well as our proposed df in terms of power when covariance estimators incorporate the Kauermann and Carroll [3] correction, whereas power gains from the use of our proposed df were more notable when using the Mancl and DeRouen [4] correction.

4.2.2 Impact of Different Corrections on Power—Power increases due to the use of our improved covariance estimator and increase in df were more notable when utilizing the Mancl and DeRouen [4] correction relative to the Kauermann and Carroll [3] correction. In Supporting Material, we show that for the small-sample settings ($N = 10$ or 20 in Scenario 1, $N = 25$ in Scenario 2), empirical means of SE estimates incorporating these different corrections are more similar in value when utilizing $\hat{\Sigma}_{WB}$ relative to $\hat{\Sigma}_{CLZ}$, with the exception of results corresponding to time in Scenario 2. The reason for this is that the influences of these corrections diminishes due to the averaging used within the meat of $\hat{\Sigma}_{WB}$ as given in Equation (4). Furthermore, the use of $\hat{\Sigma}_{WB}$ gave more accurate SE estimates on average in Scenario 1. Therefore, our proposed approach has an advantage in that it is not as sensitive with respect to this type of correction and can be more accurate. As a result, our approach can remove some of the potential conservativeness of the Mancl and DeRouen [4] correction that is observed with $\hat{\Sigma}_{CLZ}$, which can make power increases with our proposed approach more notable.

4.2.3 Overall Impact of Proposed Approach on Power—Table 3 shows that whether using $\hat{\Sigma}_{WB}$ or $\hat{\Sigma}_{CLZ}$ in the settings of Scenario 1, the empirical selection frequencies resulting from the incorporation of the Mancl and DeRouen [4] or Kauermann and Carroll [3] corrections were similar. Furthermore, use of $\hat{\Sigma}_{WB}$, relative to $\hat{\Sigma}_{CLZ}$, increased the frequency of selecting AR-1, the true structure. Although this did not appear to notably improve ESDs in many settings, the ESDs were lower when using $\hat{\Sigma}_{WB}$ and $N = 10$ and $\rho = 0.7$. As a result, the majority of the empirical power increases due to the use of our proposed approach were attributable to increases in df. As seen in Table 3, the power increases resulting from our overall proposed approach, relative to the use of $\hat{\Sigma}_{CLZ}$ for correlation selection and inference, tended to be greater when N was 10 or 20. We note that in the settings of Scenario 2, the use of $\hat{\Sigma}_{WB}$ and $\hat{\Sigma}_{CLZ}$ within correlation selection criteria resulted in very similar empirical selection frequencies (results not shown). Therefore, any power increases from our proposed approach in this scenario are due to increases in df.

We note that when $N = 10$ or 20 , empirical powers were at times slightly greater in Table 3 relative to Table 1, although results in Table 1 were based on using the true structure in each of the 1,000 simulations. The likely reason for this, as presented and explained in Supporting Material, is because our correlation selection penalty did not completely offset the induced

bias in standard error estimation resulting from correlation selection. However, results in Supporting Material show that inference is still valid in these settings.

4.2.4 Impact of the Number of Subjects—The number of subjects, N , showed to play a key role in the results, as expected. In short, the smaller (larger) N is, the greater (smaller) the potential improvement in inference when using our proposed approach. Therefore, benefits from the use of our proposed approach will only be notable when N is small, whereas no advantage will be seen for larger N . For instance, when $N = 100$, increases in df has little impact on critical values, and thus power. Furthermore, when N is this large, correlation selection criteria may already perform very well, and therefore the degree of improvement in selection accuracy of the TECM by using our proposed covariance matrix estimator may be limited. This was particularly seen in Scenario 1 when $\rho = 0.7$.

4.2.5 Summary—Our proposed method consists of the use of $\hat{\Sigma}_{WB}$ within the TECM or CIC to select a working correlation structure, and the use of $\hat{\Sigma}_{WB}$ and corresponding df for statistical inference. Although the use of $\hat{\Sigma}_{WB}$ relative to $\hat{\Sigma}_{CLZ}$ did not increase df or power for time (Scenario 2, β_1), results show that our proposed method can increase the power of tests on parameters corresponding to either time-dependent (Scenario 1, β_1 and β_2) or time-independent (Scenario 2, β_2) covariates that vary in value across subjects. Furthermore, in the studied settings these power increases resulted mostly from an increase in df due to improved estimation of $Cov(\hat{\beta})$. Finally, power increases are larger for smaller numbers of subjects and when the Mancl and DeRouen [4] correction is utilized.

5 Application

We now analyze data from the Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE) clinical trial [25]. Specifically, we utilize data from men who annually contributed Consortium to Establish a Registry for Alzheimer's Disease (CERAD) T-scores [26, 27] for three to four consecutive years. T-scores are a measure for global cognitive status [25], and higher scores imply greater cognition. We are interested in how mean T-scores change over time, in addition to the impacts of baseline age in years and estimated full-scale IQ [28].

We fit the marginal model given by

$$\mu_{ij} = \beta_0 + \beta_1 \text{time}_j + \beta_2 (\text{IQ}_i - 110) + \beta_3 (\text{Age}_i - 70); \quad j=1, \dots, n_i.$$

Here, n_i is either 3 or 4, μ_{ij} is the mean T-score for the i th subject at their j th annual visit, and $\text{time}_j = j - 1$ is the number of years from baseline. We note that an analysis utilizing 50 subjects, along with the use of the square of centered age as a covariate, can be found in [16]. However, we fit the above model using data from 25 subjects in order to demonstrate an example where our proposed method influences statistical significance at the 0.05 level. We note that with this subset of data, the square of centered age is not statistically significant for any working correlation structure we consider.

Results are given in Table 4 from the use of GEE incorporating either the independence, exchangeable, or AR-1 working correlation structures. We present regression parameter estimates and their corresponding SE estimates obtained from either $\hat{\Sigma}_{CLZ}$ or $\hat{\Sigma}_{WB}$, both of which incorporate either the Mancl and DeRouen [4] or the Kauermann and Carroll [3] correction. We also present estimated df and values of the TECM. Relevant p-values are discussed below.

For any given working correlation structure, our proposed df, resulting from the use of $\hat{\Sigma}_{WB}$, were actually a little smaller than the Pan and Wall [12] df, resulting from the use of $\hat{\Sigma}_{CLZ}$, corresponding to the test for time (β_1). However, the p-values corresponding to this two-sided test were all less than 0.01, and therefore df had no impact on statistical significance. Alternatively, df corresponding to tests for centered IQ (β_2) and age (β_3) were notably larger when utilizing our proposed df, and p-values resulting from these tests decreased when using our proposed SE estimator and df.

Similar to our findings in Scenario 2 of our simulation study, incorporation of either $\hat{\Sigma}_{CLZ}$ or $\hat{\Sigma}_{WB}$ within the TECM, regardless of whether the Mancl and DeRouen [4] or the Kauermann and Carroll [3] correction is utilized, resulted in the selection of the exchangeable correlation structure. As a result, based on a 0.05 significance level, our proposed method influenced statistical significance with respect to age. Specifically, with our proposed method, the estimated SE for β_3 and corresponding df are 0.31 (0.33) and 42.4 (42.1) when utilizing the Kauermann and Carroll [3] (Mancl and DeRouen [4]) correction. After subtracting 2 df due to considering three correlation structures for selection, the resulting p-value is 0.033 (0.045). Alternatively, the SE estimates from $\hat{\Sigma}_{CLZ}$ are 0.33 and 0.36 when utilizing the Kauermann and Carroll [3] and Mancl and DeRouen [4] correction, respectively, with corresponding Pan and Wall [12] df of 17.9 with either correction. The resulting p-values are greater than 0.05 at 0.053 and 0.074, respectively. Alternatively, if using $N - p$ df, the resulting p-values are 0.0498 and 0.071, respectively. Therefore, our proposed method does (does not) change our conclusion at the 0.05 level when compared to the use of SE estimates from $\hat{\Sigma}_{CLZ}$ with the Mancl and DeRouen [4] (Kauermann and Carroll [3]) correction and $N - p$ df.

6 Concluding Remarks

In this manuscript, we summarized methods that have been proposed to improve the small-sample validity of inference when using GEE. We then combined such methods and proposed the use of a modified, potentially more precise, empirical covariance estimator. As a result, power has the potential to increase due to an increase in df and improved regression parameter estimation via enhanced correlation selection accuracy.

We found that the potential for an increase in power with our proposed method depends on the nature of covariate values across subjects. Inference with respect to time as a covariate is not notably impacted by our proposed method. The reason for this is because when time values do not vary across subjects, our proposed covariance estimator cannot improve the precision of the corresponding standard error estimation. An explanation is provided in Section 1.4 of Supporting Material. In short, when the distribution of values for any given

covariate does not vary across subjects, the resulting formula for the variance estimate of the corresponding regression parameter estimate will not actually change when applying our proposed covariance estimator. Therefore, df will not change. Alternatively, when a covariate's value or collection of values over time vary across subjects, the variance of the corresponding regression parameter estimate will be estimated more precisely because the center of our proposed estimator pools subjects' empirical correlations, each of which corresponds to unique values for the given covariate. Therefore, our proposed method can improve df and possibly correlation structure selection, therefore increasing power. This was seen with the time-dependent covariates in Scenario 1 of our simulation study, and the baseline covariate in Scenario 2 as well as IQ and age in our application example.

Although in our simulation study power improved mostly due to increased df, this result does not imply that power will not increase in other settings due to improved correlation selection accuracy. In general, increasing correlation selection accuracy will decrease the true standard errors of regression parameter estimates, therefore increasing power. However, how much improvement can be made via enhanced correlation selection accuracy depends on how accurate correlation selection criteria already are without our modified empirical covariance estimator and how much efficiency can be gained.

In our study, we used a df penalty with the goal of ensuring valid inference. Although there were a few exceptions, this penalty worked well. Furthermore, this penalty was shown to have negligible impact in terms of power. We also note that the relative increase in power due to the use of our proposed method is more notable when using the Mancl and DeRouen [4] correction relative to the use of the Kauermann and Carroll [3] correction.

As noted by Pan [2], when outcomes are binary, it is unlikely for a common correlation structure to exist due to constraints on the correlation parameters [24, 23]. However, Pan's [2] simulation study showed that minor violations to assuming a common correlation structure may not be detrimental toward attaining valid inference. We note that Wang and Long [8] also demonstrated the same result in their simulation study in which they generated outcomes from a Poisson mixed-effect model. Similarly, results from our simulation study also suggest that our approach can be applicable with binary outcomes (see Supporting Material).

Although not our primary focus of this manuscript, we compared the use of $N - p$ and the Pan and Wall [12] df when utilizing $\hat{\Sigma}_{CLZ}$. To our knowledge, very few comparisons of these degrees of freedom methods have been published. In settings focused on cluster randomized trials with binary outcomes, Westgate's [21] simulation study showed that the use of $N - p$ df tended to work better than the Pan and Wall [12] df with respect to attaining valid inference, with the latter df approach tending towards slightly liberal inference. Similarly, in our study (see Supporting Material) we found the Pan and Wall [12] df to be more liberal than the use of $N - p$ df in the context of Scenario 1, although the Pan and Wall [12] df still worked well overall in terms of attaining valid inference. In Scenario 2, the use of $N - p$ df or the Pan and Wall [12] df resulted in similar empirical coverage probabilities and test sizes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scenario 1 empirical powers based on different standard error (SE) estimators and corresponding degrees of freedom (df) used with Wald Tests. Results are from the use of a working and true AR-1 structure with correlation parameter ρ . Empirical mean df are given in parentheses.

Table 1

ρ	β	N	KC			MD		
			df Type: $N-p$	PW	WB	$N-p$	PW	WB
0.3	β_1	10	0.05	0.08 (13.7)	0.07 (42.7)	0.05	0.06 (13.4)	0.06 (42.2)
		20	0.11	0.11 (21.6)	0.11 (77.5)	0.10	0.10 (21.2)	0.11 (77.4)
		100	0.44	0.44 (81.7)	0.45 (359.0)	0.43	0.43 (81.3)	0.44 (359.0)
	β_2	10	0.36	0.40 (13.9)	0.45 (41.5)	0.29	0.34 (13.5)	0.41 (41.0)
		20	0.70	0.70 (22.2)	0.74 (76.5)	0.67	0.67 (21.9)	0.73 (76.3)
		100	1.00	1.00 (81.3)	1.00 (359.3)	1.00	1.00 (80.9)	1.00 (359.3)
0.7	β_1	10	0.10	0.12 (13.0)	0.13 (35.4)	0.07	0.09 (12.5)	0.11 (34.4)
		20	0.21	0.21 (20.0)	0.22 (62.0)	0.18	0.18 (20.0)	0.20 (61.5)
		100	0.76	0.76 (70.8)	0.77 (274.0)	0.75	0.75 (70.3)	0.77 (273.5)
	β_2	10	0.63	0.66 (12.9)	0.73 (34.5)	0.54	0.58 (12.5)	0.70 (33.5)
		20	0.95	0.95 (20.0)	0.97 (62.4)	0.94	0.93 (19.6)	0.97 (61.8)
		100	1.00	1.00 (70.6)	1.00 (275.5)	1.00	1.00 (70.0)	1.00 (275.0)

N - Number of independent subjects

KC - The covariance matrix, and thus SE, estimator incorporates the Kauermann and Carroll [3] correction

MD - The covariance matrix, and thus SE, estimator incorporates the Manel and DeRouen [4] correction

$N-p$ - Tests utilizing $N-p$ df use empirical SE estimates obtained from $\hat{\Sigma}_{CLZ}$ which incorporates either the KC or MD correction

PW - df are obtained from the method proposed by Pan and Wall [12], and the corresponding Wald test utilizes empirical SE estimates obtained from $\hat{\Sigma}_{CLZ}$ which incorporates either the KC or MD correction

WB - Wald tests utilize our proposed df as derived in Supporting Material and SE estimates obtained from our proposed covariance matrix estimator, $\hat{\Sigma}_{WB}$ which incorporates either the KC or MD correction

Scenario 2 empirical powers based on different standard error (SE) estimators and corresponding degrees of freedom (df) used with Wald Tests. Results are from the use of a working and true AR-1 structure with correlation parameter ρ . Empirical mean df are given in parentheses.

Table 2

ρ	β	N	KC			MD		
			df Type: $N-p$	PW	WB	$N-p$	PW	WB
0.3	β_1	25	0.56	0.57 (31.3)	0.57 (31.3)	0.55	0.56 (31.3)	0.56 (31.3)
		100	0.99	0.99 (106.4)	0.99 (106.4)	0.99	0.99 (106.4)	0.99 (106.4)
	β_2	25	0.91	0.89 (17.4)	0.92 (31.2)	0.88	0.86 (16.9)	0.91 (31.1)
		100	1.00	1.00 (53.5)	1.00 (106.7)	1.00	1.00 (53.1)	1.00 (106.8)
0.7	β_1	25	0.73	0.73 (30.8)	0.73 (30.8)	0.71	0.72 (30.8)	0.72 (30.8)
		100	1.00	1.00 (106.8)	1.00 (106.8)	1.00	1.00 (106.8)	1.00 (106.8)
	β_2	25	0.71	0.68 (17.2)	0.73 (31.8)	0.66	0.64 (16.7)	0.71 (31.7)
		100	1.00	1.00 (52.1)	1.00 (107.9)	1.00	1.00 (51.7)	1.00 (107.9)

N - Number of independent subjects

KC - The covariance matrix, and thus SE, estimator incorporates the Kauermann and Carroll [3] correction

MD - The covariance matrix, and thus SE, estimator incorporates the Mancl and DeRouen [4] correction

$N-p$ - Tests utilizing $N-p$ df use empirical SE estimates obtained from $\hat{\Sigma}_{CLZ}$ which incorporates either the KC or MD correction

PW - df are obtained from the method proposed by Pan and Wall [12], and the corresponding Wald test utilizes empirical SE estimates obtained from $\hat{\Sigma}_{CLZ}$ which incorporates either the KC or MD correction

WB - Wald tests utilize our proposed df as derived in Supporting Material and SE estimates obtained from our proposed covariance matrix estimator, $\hat{\Sigma}_{WB}$, which incorporates either the KC or MD correction

Table 3

Scenario 1 empirical frequencies of the trace of the empirical covariance matrix (TECM) criterion selecting each working correlation structure out of 1,000 replications, and resulting empirical standard deviations (ESD) of parameter estimates and empirical powers from Wald tests. The true correlation structure is AR-1 with parameter ρ .

ρ	N	Covariance Estimator used within the TECM, and df Method for Test	Selection Frequencies				ESD		Power*	
			Ind	Exch	AR-1	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_1$	$\hat{\beta}_2$	
0.3	10	$\hat{\Sigma}_{CLZ}$ with KC, PW df	371	211	418	0.545	0.545	0.09	0.41	
		$\hat{\Sigma}_{CLZ}$ with MD, PW df	371	218	411	0.541	0.545	0.06	0.35	
		$\hat{\Sigma}_{WGB}$ with KC, WB df	306	234	460	0.544	0.547	0.07	0.47	
		$\hat{\Sigma}_{WGB}$ with MD, WB df	290	245	465	0.546	0.546	0.06	0.44	
		$\hat{\Sigma}_{CLZ}$ with KC, PW df	248	218	534	0.382	0.382	0.12	0.70	
	20	$\hat{\Sigma}_{CLZ}$ with MD, PW df	244	227	529	0.382	0.382	0.10	0.67	
		$\hat{\Sigma}_{WGB}$ with KC, WB df	141	214	645	0.380	0.379	0.12	0.75	
		$\hat{\Sigma}_{WGB}$ with MD, WB df	135	236	629	0.380	0.378	0.11	0.73	
		$\hat{\Sigma}_{CLZ}$ with KC, PW df	13	118	869	0.162	0.166	0.43	1.00	
		$\hat{\Sigma}_{CLZ}$ with MD, PW df	12	124	864	0.162	0.167	0.43	1.00	
0.7	100	$\hat{\Sigma}_{WGB}$ with KC, WB df	0	42	958	0.162	0.166	0.45	1.00	
		$\hat{\Sigma}_{WGB}$ with MD, WB df	0	43	957	0.162	0.166	0.45	1.00	
		$\hat{\Sigma}_{CLZ}$ with KC, PW df	66	227	707	0.403	0.402	0.13	0.65	
		$\hat{\Sigma}_{CLZ}$ with MD, PW df	65	258	677	0.400	0.404	0.10	0.59	
		$\hat{\Sigma}_{WGB}$ with KC, WB df	13	185	802	0.386	0.390	0.14	0.74	
	20	$\hat{\Sigma}_{WGB}$ with MD, WB df	12	216	772	0.391	0.394	0.11	0.71	
		$\hat{\Sigma}_{CLZ}$ with KC, PW df	3	122	875	0.266	0.265	0.20	0.93	
		$\hat{\Sigma}_{CLZ}$ with MD, PW df	3	144	853	0.267	0.265	0.18	0.92	
		$\hat{\Sigma}_{WGB}$ with KC, WB df	0	71	929	0.261	0.262	0.22	0.97	
		$\hat{\Sigma}_{WGB}$ with MD, WB df	0	81	919	0.261	0.263	0.21	0.97	

ρ	N	Covariance Estimator used within the TECM, and df Method for Test	Selection Frequencies			ESD		Power*	
			Ind	Exch	AR-1	$\hat{\beta}_1$	$\hat{\beta}_2$	β_1	β_2
100		$\hat{\Sigma}_{CLZ}$ with KC, PW df	0	6	994	0.112	0.112	0.76	1.00
		$\hat{\Sigma}_{CLZ}$ with MD, PW df	0	6	994	0.112	0.112	0.75	1.00
		$\hat{\Sigma}_{WB}$ with KC, WB df	0	0	1000	0.112	0.112	0.77	1.00
		$\hat{\Sigma}_{WB}$ with MD, WB df	0	0	1000	0.112	0.112	0.77	1.00

N - number of independent subjects; Ind - Independence; Exch - Exchangeable; df - degrees of freedom

$\hat{\Sigma}_{CLZ}$ - Empirical covariance estimator defined in Equation (2) that does not use additional assumptions as in $\hat{\Sigma}_{WB}$

$\hat{\Sigma}_{WB}$ - Empirical covariance estimator defined in Equation (3) that assumes the marginal variances of the outcomes are modeled correctly and there is a common correlation structure for each subject.

KC - The covariance matrix estimator incorporates the Kauermann and Carroll [3] correction

MD - The covariance matrix estimator incorporates the Mancini and DeRouen [4] correction

PW - df are obtained from the method proposed by Pan and Wall [12]

WB - df are obtained using the method we propose in this manuscript (df given in Supporting Material)

Power* - Wald tests, from which empirical powers are obtained, utilize standard error estimates obtained from the covariance estimator incorporated within the corresponding TECM.

Table 4

Application example analysis results.

		Estimated Standard Errors and Degrees of Freedom (Parentheses) Obtained From the Given Estimators				
Working Structure	Parameter	$\hat{\beta}$	$\hat{\Sigma}_{CLZ}$ with KC (PW)	$\hat{\Sigma}_{CLZ}$ with MD (PW)	$\hat{\Sigma}_{WB}$ with KC (WB)	$\hat{\Sigma}_{WB}$ with MD (WB)
Independence	β_0	49.1	1.72 (50.7)	1.81 (51.4)	1.73 (56.9)	1.82 (57.6)
	β_1	2.60	0.55 (34.1)	0.57 (35.1)	0.55 (31.4)	0.57 (31.9)
	β_2	0.43	0.21 (11.8)	0.24 (11.4)	0.22 (36.9)	0.24 (36.9)
	β_3	-0.70	0.32 (17.5)	0.35 (17.5)	0.31 (40.8)	0.33 (40.7)
	TECM		3.41	3.79	3.43	3.82
Exchangeable	β_0	49.6	1.68 (45.3)	1.77 (47.0)	1.69 (50.6)	1.79 (51.8)
	β_1	1.95	0.52 (19.8)	0.53 (19.9)	0.52 (15.6)	0.53 (14.9)
	β_2	0.43	0.22 (12.5)	0.24 (12.1)	0.23 (37.2)	0.24 (37.1)
	β_3	-0.69	0.33 (17.9)	0.36 (17.9)	0.31 (42.4)	0.33 (42.1)
	TECM		3.24	3.60	3.28	3.66
AR-1	β_0	49.5	1.73 (45.2)	1.82 (47.4)	1.76 (44.0)	1.86 (44.8)
	β_1	1.95	0.61 (18.9)	0.62 (19.2)	0.57 (17.3)	0.58 (16.6)
	β_2	0.38	0.23 (9.7)	0.26 (9.6)	0.23 (31.0)	0.25 (30.1)
	β_3	-0.71	0.33 (19.4)	0.36 (19.3)	0.31 (38.2)	0.33 (36.6)
	TECM		3.52	3.92	3.57	3.99

TECM - trace of the empirical covariance matrix, given for each empirical covariance matrix estimator

$\hat{\Sigma}_{CLZ}$ - Empirical covariance estimator defined in Equation (2) that does not use additional assumptions as in $\hat{\Sigma}_{WB}$

$\hat{\Sigma}_{WB}$ - Empirical covariance estimator defined in Equation (3) that assumes the marginal variances of the outcomes are modeled correctly and there is a common correlation structure for each subject.

KC - The covariance matrix estimator incorporates the Kauermann and Carroll [3] correction

MD - The covariance matrix estimator incorporates the Mancl and DeRouen [4] correction

PW - Degrees of freedom are obtained from the method proposed by Pan and Wall [12]

WB - Degrees of freedom are obtained using the method we propose in this manuscript (df given in Supporting Material)