

Modeling Longitudinal Binary Outcomes in a Small Matched-Pair Sample with Application to Cardiovascular Data: A Simulation Study

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Abstract

This study aimed to address the challenge of modeling small sample matched-pair longitudinal data in cardiovascular research. The independent working correlation structure in Generalized Estimating Equations (GEE), a robust method widely used for modeling endogenous follow-up data, relies on large-sample theory. Prior research has noted significant constraints due to small sample sizes for continuous outcomes. We evaluated the performance and validity of the GEE method and the two-stage quasi-least squares (QLS) approach in analyzing small matched-pair longitudinal binary data, particularly focusing on the interaction effect between bicuspid aortic valve (BAV) and time on aortic root size post-surgery. Hospital cohorts with longitudinal outcomes across two exposure groups were matched using propensity scores based on baseline characteristics to eliminate potential confounding effects, which is followed by GEE fit assuming that working correlation structure is AR1 to get a set of regression coefficients for simulation parameters. Simulations were designed to mimic real-world dropout processes, where previous survival outcomes and associated covariates influence longitudinal outcomes. Standard errors were adjusted by degrees of freedom to prevent underestimation by the sandwich estimator. Results: The QLS method demonstrated superior performance, with mean estimates closer to the true coefficients and narrower confidence intervals than GEE, while GEE provided more accurate estimation for the interaction effect but exhibited higher variability in estimates. Both methods struggled to capture the effect of time. Including confounding covariates did not significantly impact performance. QLS provided more consistent estimates across different correlation structures but with higher bias. Conclusion: Proper specification of the correlation structure is crucial for the robust analysis of small sample longitudinal

data. For studies with small sample sizes and complex correlation structures, QLS may offer a more reliable alternative by providing consistent estimates with lower variability. These findings underscore the importance of methodological considerations in longitudinal data analysis and offer guidance for selecting appropriate analytical approaches.

1 Introduction

The generalized estimating equations (GEE) method is commonly used in longitudinal studies where the response variable for each subject is measured repeatedly over time (Liang and Zeger, 1986a). It is an extension of the quasi-likelihood method that models the marginal expectation of the response, either discrete or binary, as a function of a set of explanatory variables (Agresti, 2007). Instead of assuming a particular type of distribution for the outcome Y , each marginal mean is linked to a linear predictor and educated guess for the variance-covariance structure, which accounts for the temporal correlation among repeated measurements. Since there is no need to specify the random effects for individual subjects or clusters, GEE provides an average response in the population rather than individual-specific effects.

Our motivation stems from the work which assessed the natural history of the aortic root in patients with bicuspid versus tricuspid aortic valves (BAVs vs. TAVs) after replacement of the aortic valve and ascending aorta at the Peter Munk Cardiac Center (Hui et al., 2018). The aorta is the main artery that carries blood from the heart’s left ventricle to the rest of the human body. According to the 2014 ESC guidelines on diagnosing and treating aortic diseases, aorta dilatation is a clinical condition with aorta diameter greater than 40 mm, irrespective of body surface area. It is commonly present in patients with BAV, a congenital heart defect when the aortic valve has only two leaflets instead of three and affects approximately 1-2% of the general population (Wang et al., 2021). Patients with aortic diameter exceeding 4.5 mm are usually associated with ascending aortic events. Evidence showed that the dilation of aortic root cannot be suppressed even after AVR (Andrus et al., 2003). Still, other researchers found that the ascending aorta dilatation rate was similar between the BAV and TAV post-surgery (Kim et al., 2020).

Given that BAV is a congenital cardiac abnormality, conducting randomized controlled trials is not feasible. Researchers often pair BAV patients with TAV patients using propensity score matching (PSM) to assess the natural history of aortic root size changes. PSM is critical in this context as it balances observed covariates between BAV and TAV groups, reducing confounding bias and enhancing the accuracy of treatment effect estimates. This technique allows for valid comparisons in observational studies, addressing selection bias and leading to more reliable conclusions about the natural history of aortic root size changes post-surgery. In practice, patients with and without exposure to interest are matched on important confounding factors such as age, sex, and calendar time

and compared for the incidence of outcomes (Iwagami and Shinozaki, 2022). In such a scenario, two distinct correlations exist: the correlation between units within the matched pair and the correlation between the temporal observations on the same patient.

The study investigators collected participant-level demographics, health outcomes, and each participant’s follow-up imaging data after the replacement of the aortic valve (AVR) and ascending aorta (RAA) from January 1900 to December 2010. This cohort consists of 406 patients, 244 of whom had follow-up measurements. Among those with follow-up visits, 172 (70.5%) patients had BAV, and the rest had TAV. Our primary outcome is whether or not the aortic root dimensions exceeded a diameter of 45 mm after the surgery. Although the data include records of patients’ vitals, only the follow-up measurements of the aortic root size and baseline covariates, including age, sex, and body surface area (BSA), are included in this study.

The first consideration in GEE analysis is the potential issue of covariate endogeneity. This concept describes the scenario when the response at time t predicts the covariate value at times $s > t$ (Diggle et al., 2002). The issue arises because the abnormal aortic root size is associated with a higher risk of death (Kitagawa et al., 2013), and the occurrence of death informs that there is no stochastic process of the deformation. The interaction effect between response and covariates is called *feedback* (Zeger and Liang, 1991). It has been shown that, based on the large-sample theory, using GEE with a working independence correlation structure can provide unbiased estimation (Diggle et al., 2002, @LiangZeger1986). However, the sample sizes in cardiovascular research are limited and mid-term follow-ups are incomplete due to the rarity of disease in practice. The validity of GEE with a working independence correlation structure remains unknown. The second consideration is that GEE methods within the existing R package, i.e., **geepack**, only account for the correlation between repeated measurements within one subject but ignore the correlation between matched pairs.

This report focuses on matched longitudinal binary data with covariate endogeneity and informative dropouts. We aim to explore the validity of GEE estimates for small sample matched-pair binary outcomes and compare the estimation results with the two-stage quasi-least squares (QLS) method (Mitani et al., 2019). In section 2, notations and assumptions are first presented, followed by a description of the issue with the correlation structure within the GEE framework, the construction of the two-stage QLS method, and the pre-processing of the motivational data. The simulation study design is presented in section 3. Section 4 presents an analysis of the motivational data and simulation results. Finally, we conclude this report with a discussion in section 5.

2 Methods

2.1 Notation and Assumptions

Consider a longitudinal matched data set in which subjects are grouped into pairs, and each subject contributes repeated observations of unique aortic root diameter. Let $Y'_{ij} = (Y_{ij1}, Y_{ij2}, \dots, Y_{ijt_{ij}})$ be a vector of measurements for subject j in matched pair i at times $t_{ij1}, t_{ij2}, \dots, t_{ijT}$, where $t_{ij1} < t_{ij2} < \dots < t_{ijT}$; $i = 1, \dots, m$; $j = 1, 2$; $k = 1, \dots, T$. Associated with each Y_{ijk} is a vector of covariates $X'_{ijk} = (X_{ijk1}, X_{ijk2}, X_{ijk3})$ corresponding to BAV (exposure), *time*, and the interaction between BAV and *time*. Note that BAV is the exposure variable which is diagnosed before this study and does not change by time. Additionally, since different patients may have different follow-up intervals, we define *time* as the number of visits. The outcome Y_{ijk} have mean and variance

$$E(Y_{ijk}|X_{ijk}) = \mu_{ijk} \quad \text{and} \quad \text{Var}(Y_{ijk}) = \mu_{ijk}(1 - \mu_{ijk}) = h(\mu_{ijk})$$

Our analysis goal is to examine the effect of these covariates on the marginal mean of the binary outcome through $g^{-1}(X'_{ijk}\beta)$, where $\beta = (\beta_0, \beta_1, \beta_2, \beta_3)$ are unknown regression coefficients and $g(\cdot)$ is the invertible link function which is defined as

$$\begin{aligned} g(\mu_{ijk}) &= \log\left(\frac{\mu_{ijk}}{1 - \mu_{ijk}}\right) \\ &= \beta_0 + \beta_1 \cdot \text{BAV}_{ijk} + \beta_2 \cdot \text{Time}_{ijk} + \beta_3 \cdot (\text{BAV}_{ijk} \times \text{Time}_{ijk}) \\ &= X'_{ijk}\beta. \end{aligned}$$

We assume that observations from different matched pairs are independent but are correlated within the same pair. The variance matrix of $Y'_i = (Y'_{i1}, Y'_{i2})$ is given by

$$\Sigma_i = A_i^{1/2}(\beta)F_i(\Gamma)A_i^{1/2}(\beta)$$

where $F_i(\Gamma)$ is the positive definite working correlation matrix of the vector of outcome for pair i , Γ is a vector of unknown correlation parameters, and

$$A_i(\beta) = \text{diag}\{A_{i1}(\beta), A_{i2}(\beta)\} \tag{1}$$

$$A_{ij}(\beta) = \text{diag}\{h(\mu_{ij1}), h(\mu_{ij2}), \dots, h(\mu_{ijT})\}. \tag{2}$$

2.2 Generalized estimating equations (GEE)

Without a specific assumption about the likelihood function, generalized estimating equations (GEE) accounts the covariance structure of the repeated measures by specifying a working correlation matrix, $R(\alpha)$, which describes the

correlation between repeated measures on the same subject. This paper focuses on the following three working correlations:

$$\begin{array}{ccc}
\begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \end{bmatrix} & \begin{bmatrix} 1 & \alpha & \cdots & \alpha \\ \alpha & 1 & \cdots & \alpha \\ \vdots & \vdots & \ddots & \vdots \\ \alpha & \alpha & \cdots & 1 \end{bmatrix} & \begin{bmatrix} 1 & \alpha & \cdots & \alpha^{t_{ij}-1} \\ \alpha & 1 & \cdots & \alpha^{t_{ij}-2} \\ \vdots & \vdots & \ddots & \vdots \\ \alpha^{t_{ij}-1} & \alpha^{t_{ij}-2} & \cdots & 1 \end{bmatrix} \\
\text{(Independent)} & \text{(Exchangeable)} & \text{(AR1)}
\end{array}$$

. The independent working correlation assumes no correlation between repeated measures. With a correlation coefficient α , the exchangeable working correlation assumes that the correlation between any pair of repeated measurements are constant at α , whereas the autoregressive order one (AR1) working correlation structure assumes correlation decreases exponentially with the time lag between measures.

GEE approach accounts for overdispersion or underdispersion by correcting the variance using a dispersion parameter

$$\text{Var}(Y_{ijk})^* = \phi \text{Var}(Y_{ijk}) = \phi h(\mu_{ijk})$$

Since our outcome is binary, the dispersion parameter ϕ equals to 1.

The iterative process starts with initial guesses for the regression coefficients $\beta^{(0)}$ and the correlation parameters $\alpha^{(0)}$. It is followed by the computation of initial marginal expectation $\mu_{ijk}^{(0)} = g^{-1}(X_{ijk}^T \beta^{(0)})$, where g^{-1} is the inverse of the link function. Then, the iterative process mainly consists of two steps: (1) update the working correlation matrix using the sample data. (2) update the regression coefficients.

2.2.1 Update the Working Correlation Matrix

To update the working correlation matrix, we first compute the residuals, $r_{ijk}^{(m)} = Y_{ijk} - \mu_{ijk}^{(m)}$, based on the current estimates of the marginal means for each observation. Then, we estimate the correlation parameters using the residuals and construct the working correlation matrix $R_i^{(m)}(\alpha^{(m)})$ using the updated correlation parameters.

2.2.2 Update the Regression Coefficients

The problem with GEE approach is that it does not account for the correlation between subjects within the same matched pair, so the variance matrix is simplified to

$$\Sigma_i(\alpha) = A_i^{1/2}(\beta) R(\alpha) A_i^{1/2}(\beta) \quad (3)$$

where $A_i^{1/2}$ is defined in (1). Then, the score function and the information matrix can be calculated using the current estimates (Zeger et al., 1988):

$$S(\beta) = \sum_{i=1}^m D_i^T \Sigma_i^{-1}(\alpha)(Y_i - \mu_i) \quad (4)$$

$$I(\beta) = \sum_{i=1}^m D_i^T \Sigma_i^{-1}(\alpha) D_i \quad (5)$$

where

$$D_i = \frac{\partial U_i}{\partial \beta} = \frac{\exp(X_i \beta)}{1 + \exp(X_i \beta)}. \quad (6)$$

The new set of regression coefficients are obtained by solving the score function, which are then used to calculate the new marginal means.

The final estimates of the regression coefficients β can be obtained by repeat the above process until convergence is achieved (Liang and Zeger, 1986b). This iterative process ensures that the correlation structure and the regression coefficients are appropriately updated using the sample data, resulting in consistent and efficient parameter estimates in the presence of correlated repeated measures.

However, it has been shown that the sandwich estimator tends to underestimate standard errors (SEs) when the size sample data is small (Mitani et al., 2019). To overcome this issue, we can adjust the sandwich estimator by degrees of freedom (MacKinnon and White, 1985):

$$\Sigma_{DF} = \left(\frac{2m}{2m - p}\right) \Sigma \quad (7)$$

where $2m$ represents the number of patients, p is the number of regression parameters.

2.3 Quasi-least squares (QLS)

Quasi-least squares (QLS) is a two-stage approach for estimating the correlation parameters in the framework of generalized estimating equations (GEE). The method involves estimating the regression parameters and the correlation structure in two distinct stages. Proposed by Chaganty (1997), the two-stage QLS method assumes that the covariance matrix are functions of the regression parameters and independent of the dispersion parameter ϕ . Additionally, the off-diagonal elements are functions of some unknown nuisance parameters. The first stage mainly aims to estimate the regression parameters by minimizing the score function, which is consistent with the GEE approach. The difference is that the QLS method solves an unbiased estimating equation for α , whereas the GEE method implements moment estimates of the correlation parameters (Xie and Shults, 2009). The second stage refines the estimates of the correlation

parameters based on the residuals from the first stage and updates the working correlation matrix. By iterating between these two stages, the two-stage QLS approach ensures robust and efficient estimates of the regression parameters while appropriately accounting for the correlation within the data.

This study adopted the method proposed by [Shults and Morrow \(2002\)](#) which specified the working correlation structure by incorporating both intravisit and intrapair correlations using equicorrelated matrices and the Kronecker product. Let the working correlation parameter $\Gamma' = (\tau', \alpha')$ where $\tau' = (\tau_1, \dots, \tau_m)$ account for the correlation between subjects for each matched pairs and $\alpha' = (\alpha_1, \alpha_2)$ is the vector of correlation coefficients for longitudinal measurements within the a subject in a pair. In this study, we assume that the intra-pair correlations are consistent across different pairs, that is, $\tau_1 = \tau_2 = \dots = \tau_m = \tau$. Let $R_i(\alpha) = \{r_{jk}^i(\alpha)\}$ be a $T \times T$ intravisit working correlation matrix for outcomes collected on subjects j from pair i and $Q_i(\tau)$ be a 2×2 equicorrelated working correlation matrix with all off-diagonal elements equal to τ_i . We assume that $F_i(\Gamma)$ is the Kronecker product of $Q_i(\tau)$ and $R_i(\alpha)$, denoting as $Q_i(\tau) \otimes R_i(\alpha)$.

Let z_{ijk} be the standardized residual for the k -th visit on the j -th subject from the i -th pair, written as

$$z_{ijk} = \frac{Y_{ijk} - \mu_{ijk}}{\sqrt{h(\mu_{ijk})}}.$$

Let Z'_{ij} be a vector of standardized residuals and U'_{ij} be a vector of mean values of longitudinal outcomes for the j -th subject form the i -th pair, then $Z'_i(\beta) = (Z'_{i1}, Z'_{i2})$ is a vector of all standardized residuals and $U'_i = (U'_{i1}, U'_{i2})$ is a vector of all expected outcomes within i -th pair. Now, the generalized error sum of squares is expressed as

$$Q(\beta, \Gamma) = \sum_{i=1}^m Z'_i(\beta) F_i^{-1}(\Gamma) Z_i(\beta)$$

2.3.1 Estimation of β

The estimating equation for β can be obtained by taking the partial derivative of $Q(\beta, \Gamma)$ with respect to β and setting it equal to 0:

$$\begin{aligned} \frac{\partial Q(\beta, \Gamma)}{\partial \beta} &= 2 \sum_{i=1}^m D'_i(\beta) F_i^{-1}(\Gamma) Z_i(\beta) \\ &= 2 \sum_{i=1}^m D'_i(\beta) F_i^{-1}(\Gamma) \left(\frac{Y_i - U_i}{\sqrt{h(U_i)}} \right) \end{aligned}$$

Then, we have

$$\sum_{i=1}^m D'_i(\beta) F_i^{-1}(\Gamma) \left(\frac{Y_i - U_i}{\sqrt{h(U_i)}} \right) = 0, \quad (8)$$

where D_i is defined in (6).

2.3.2 Estimation of Γ

The partial derivative of $Q(\beta, \Gamma)$ with respect to Γ can be divided into two parts: taking partial derivative with respect to τ and α separately. Since the stage one estimation is asymptotically biased (Chaganty and Shults, 1999), the estimation for τ and α involves two stages for each.

Stage One Estimators

As defined earlier,

$$Q_i(\tau) = \begin{bmatrix} 1 & \tau \\ \tau & 1 \end{bmatrix} \Rightarrow Q_i^{-1}(\tau) = \frac{1}{1-\tau^2} \begin{bmatrix} 1 & -\tau \\ -\tau & 1 \end{bmatrix}$$

Let $q_1 = \frac{1}{1-\tau^2}$ and $q_2 = \frac{-\tau}{1-\tau^2}$, then we can obtain the first stage estimator for τ by

$$\frac{\partial}{\partial \tau} \left\{ \sum_{i=1}^m (Z_{i1} \ Z_{i2}) \left[\begin{pmatrix} q_1 & q_2 \\ q_2 & q_1 \end{pmatrix} \otimes R_i^{-1}(\alpha) \right] \begin{pmatrix} Z_{i1} \\ Z_{i2} \end{pmatrix} \right\} = 0 \quad (9)$$

$$\sum_{i=1}^m \frac{\partial}{\partial \tau} [q_1(Z_{i1}R_i^{-1}Z_{i1} + Z_{i2}R_i^{-1}Z_{i2}) + 2q_2(Z_{i1}R_i^{-1}Z_{i2})] = 0 \quad (10)$$

Let $a_1 = (Z_{i1}R_i^{-1}Z_{i1} + Z_{i2}R_i^{-1}Z_{i2})$ and $a_2 = (Z_{i1}R_i^{-1}Z_{i2})$, the stage one estimator for τ can be obtained by solving the equation (10):

$$\hat{\tau}_0 = \frac{a_1 - \sqrt{a_1^2 - 4a_2^2}}{2a_2}$$

Given that all the subjects from the motivational study underwent the aortic root replacement surgery, it is reasonable to believe that the correlation of longitudinal measurements is decreasing as time passes. Therefore, AR1 is assumed to be the true working correlation structure. Then, a closed-form solution for stage one α is:

$$\hat{\alpha}_0 = \frac{F_a + \sqrt{(F_1 + F_b)(F_a - F_b)}}{F_b} \quad (11)$$

where

$$F_a = \sum_{i=1}^N \frac{1}{2} \sum_{j=1}^2 \frac{1}{t_{ij}} \left[\sum_{k=1}^{t_{ij}} Z_{ijk}^T C_i^{-1} Z_{ijk} + \sum_{k=2}^{t_{ij}-1} Z_{ijk}^T C_i^{-1} Z_{ijk} \right]$$

and $F_b = 2 \sum_{i=1}^N \frac{1}{2} \sum_{j=1}^2 \frac{1}{t_{ij}} \sum_{k=1}^{t_{ij}-1} Z_{ijk}^T C_i^{-1} Z_{ijk+1}$. The closed form solution for the stage two estimator of α is given by (Mitani et al., 2019):

$$\hat{\alpha} = \frac{2\hat{\alpha}_0}{1 + \hat{\alpha}_0^2} \quad (12)$$

. Details of the derivations for equation (11) is shown in the Appendix A.

2.4 Modeling Motivational Data

To model the motivational data, we first selected all patients who had at least one follow-up visit with baseline measurement being taken at the day of operation. Then, a binary outcome was created by setting it to 1 if the current root size measurement is over 45 mm or the growth from the previous measure is over 5 mm, and 0 otherwise. A maximal of 6 records (including the baseline) for each patient were kept for further analysis. Then, assuming that dropouts follows Weibull distribution, 5 survival models were fitted from visit 2 to 6. The fitting coefficients were extracted for simulation. Next, a logistic regression model is fitted on the data which included the baseline measurements so that we can pair BAV patients with TAV patients using the `pairmatch` function from the R package `optmatch` (Hansen and Klopfer, 2006). Then, we applied the function `geeglm` from the R package `geepack` on the matched data set to produce the estimation results using independence, exchangeable, and AR1 working correlation structures. Finally, customized functions for implementing QLS are applied on the matched data.

3 Simulation Study

3.1 Full Data Simulation

The simulation process for generating one set of cohort data involves several steps to model both covariates and binary outcomes for each patient. For each patient, we first simulated baseline covariates, including age, sex, and body surface area (BSA), by assuming a normal distribution for continuous data and a binomial distribution for binary data. To calculate the probability of having BAV, we used a logistic regression model of the form:

$$\Pr(\text{BAV} = 1 | \text{Age, Sex, BSA}) = \frac{\exp(\gamma_0 + \gamma_1 \cdot \text{Age} + \gamma_2 \cdot \text{Sex} + \gamma_3 \text{BSA})}{1 + \exp(\gamma_0 + \gamma_1 \cdot \text{Age} + \gamma_2 \cdot \text{Sex} + \gamma_3 \text{BSA})}$$

where $\gamma_0 = -0.407$, $\gamma_1 = -0.071$, $\gamma_2 = 1.231$, and $\gamma_3 = 3.038$. This probability is then used to generate the exposure variable, BAV, under binomial distribution. To simulate longitudinal matched data with binary outcomes, the marginal probability of having positive outcome is obtained by using another logistic regression model that includes BAV, visit times, and their interaction

$$\Pr(Y = 1 | \text{BAV, Visit, BAV} \times \text{Visit}) = \frac{\exp(\beta_0 + \beta_1 \cdot \text{BAV} + \beta_2 \cdot \text{Visit} + \beta_3 \cdot \text{BAV} \cdot \text{Visit})}{1 + \exp(\beta_0 + \beta_1 \cdot \text{BAV} + \beta_2 \cdot \text{Visit} + \beta_3 \cdot \text{BAV} \cdot \text{Visit})}.$$

where $\beta_0 = -1.784$, $\beta_1 = -1.077$, $\beta_2 = -0.042$ and $\beta_3 = 0.192$.

Each subject is assumed to have six visits, including the baseline measurement, so six marginal probabilities are produced through this process. The true correlation among longitudinal measurements is set to be 0.3, and the working

covariance is assumed to follow a first-order autoregressive structure, where correlations decrease with the distance between observations. Finally, the binary longitudinal outcomes are generated using these marginal probabilities with the `cBern` function within the `CorBin` package in R. This package, developed by [Wei Jiang and Zhao \(2021\)](#), simulates binary outcomes by ensuring a positive definite correlation matrix and restricting the range of correlation coefficients using Prentice constraints ([Prentice, 1988](#)).

3.2 Informative Dropout Simulation and Propensity Score Matching

To simulate the informative dropouts, we first modeled the dropout pattern by fitting the motivational data using survival models at every visit except the baseline and the last measurement. For each visit, the status indicator was set to 1 if the maximum number of visits for the subject was the current visit, indicating dropout from the study with no further follow-up measurements. For example, the first survival model was fitted at visit 2 since visit 1 is the baseline measurement, and subjects with a total of 2 visits were assigned a status of 1. The event time was defined as the total number of visits. Given that the total number of visits was 6, four survival models were fitted to the real data. The fitting coefficients, including scale and shape parameters, were extracted from these models. These parameters were then used in the `simsurv` function to simulate dropouts at each follow-up visit for the simulated data ([Brilleman et al., 2020](#)). Once the dropout process is completed, propensity scores are calculated based on the logistic regression with the three baseline covariates, which are then been applied with the `pairmatch` function in the `optmatch` R package to match BAV subjects with TAV subjects. Then, we applied QLS with independence, AR1, and exchangeable working correlation structures to estimate the regression coefficients. We also applied GEE functions from existing R package `geepack` with the three working correlation structures ([Højsgaard et al., 2006](#)).

We simulated 1,000 data sets, each containing 250 subjects with up to 6 observations per subject, using the described simulation process. For each simulation and method, we computed the mean estimates, the mean standard errors, mean robust standard errors (MSEs), the standard deviations (SD), mean bias, and mean relative bias for each regression coefficient estimate. The mean bias was obtained by calculating the difference between the mean estimates and the respective true value, which was then divided by the true value to obtain the mean relative bias. The coverage probability was determined by calculating the proportion of the 95% confidence intervals that included the respective true parameter values among the 1,000 fitting results.

4 Results

4.1 Analysis of Motivational Data

Table 1 compares the estimates, standard errors (SE), and SE adjusted for degrees of freedom (SE-DF) for the GEE and QLS methods across different working correlation structures in modeling the binary outcome of aortic root diameter in BAV patients using data from the Peter Munk Cardiac Center. Within each method, parameter estimates are stable across correlation structures, showing minor variations. The GEE method estimates for β_1 (BAV) range from -1.093 to -1.117, while QLS estimates range from -0.108 to -0.071. For β_2 (Visit), GEE estimates range from -0.063 to -0.042, and QLS estimates range from -0.005 to 0.011. The interaction term β_4 shows a positive effect across both methods, with GEE estimates ranging from 0.192 to 0.224 and QLS estimates ranging from 0.003 to 0.026. The correlation parameter α are all around 0.01 and 0.55 for GEE and QLS, respectively. Specifying the working correlation to be independence is actually assuming that there is no correlation among repeated measurements, the QLS approach estimated the intra-pair correlation to be 0.494 which is higher than estimates using the other two working correlations. The intra-pair correlation is smallest when the specified working correlation is consistent with the true working correlation at around 0.307.

Across methods, there are notable differences in parameter estimates within the same correlation structure. GEE consistently shows stronger associations for BAV status and its interaction with time compared to QLS, which yields more conservative estimates. The GEE method suggests a stronger negative association between BAV status and the binary outcome and a positive interaction effect between visit and BAV status, while the QLS method indicates smaller effects.

Table 1: Comparison of Estimations from GEE and QLS using longitudinal data from the Peter Munk Cardiac Center.

Method	Parameter	Independence			AR1			Exchangeable		
		Estimate	SE	SE-DF	Estimate	SE	SE-DF	Estimate	SE	SE-DF
GEE	β_0 (Intercept)	-1.737	0.632	0.663	-1.784	0.631	0.662	-1.750	0.619	0.649
	β_1 (BAV)	-1.093	0.811	0.850	-1.077	0.811	0.851	-1.117	0.787	0.825
	β_2 (Visit)	-0.052	0.155	0.163	-0.042	0.154	0.162	-0.063	0.171	0.179
	β_4 (Visit \times BAV)	0.195	0.183	0.192	0.192	0.182	0.191	0.224	0.191	0.200
	α				0.093	0.111		0.081	0.063	
	τ									
QLS	β_0 (Intercept)	0.115	0.536	0.563	0.096	0.503	0.527	0.130	0.482	0.505
	β_1 (BAV)	-0.084	0.469	0.492	-0.071	0.482	0.505	-0.108	0.401	0.420
	β_2 (Visit)	0.011	0.163	0.171	0.011	0.124	0.130	-0.005	0.106	0.111
	β_4 (Visit \times BAV)	0.003	0.189	0.198	0.007	0.202	0.212	0.026	0.125	0.131
	α				0.535			0.556		
	τ	0.494			0.307			0.354		

4.2 Simulation Results

All 1000 simulations converged for both GEE and QLS fits. Each simulation was checked for extreme values. Seventy-one simulations showed extremely large standard errors when fitted with GEE, while only nine simulations exhibited extreme standard errors using the QLS approach. These problematic simulations were removed from further analysis.

Figure 1 shows the average regression coefficient estimates from 1000 simulations for the GEE (left three columns) and QLS (right three columns) methods. The estimates are presented for three covariates: BAV, Visit, and their interaction ($BAV \times Visit$). Each dot represents the mean estimate across simulations, with colours indicating different working correlation structures: AR1 (red), Exchangeable (blue), and Independence (green). The panel labels indicate that the 95% confidence intervals in the first row are based on empirical standard errors, whereas the second row uses standard errors corrected by degrees of freedom. The black dashed line marks the true coefficient values used in the simulations. In general, QLS shows smaller variability in estimates compared to GEE, and both methods fail to capture the true coefficient for the effect of Visit regardless of the adjustment for standard errors. The mean estimates for the effect of BAV using QLS are more accurate and have less variability, while the mean estimates for the interaction effect using the GEE approach are closer to the true value, although they show greater variability. More details about accurate true parameter coverage probabilities can be found in the Appendix B.

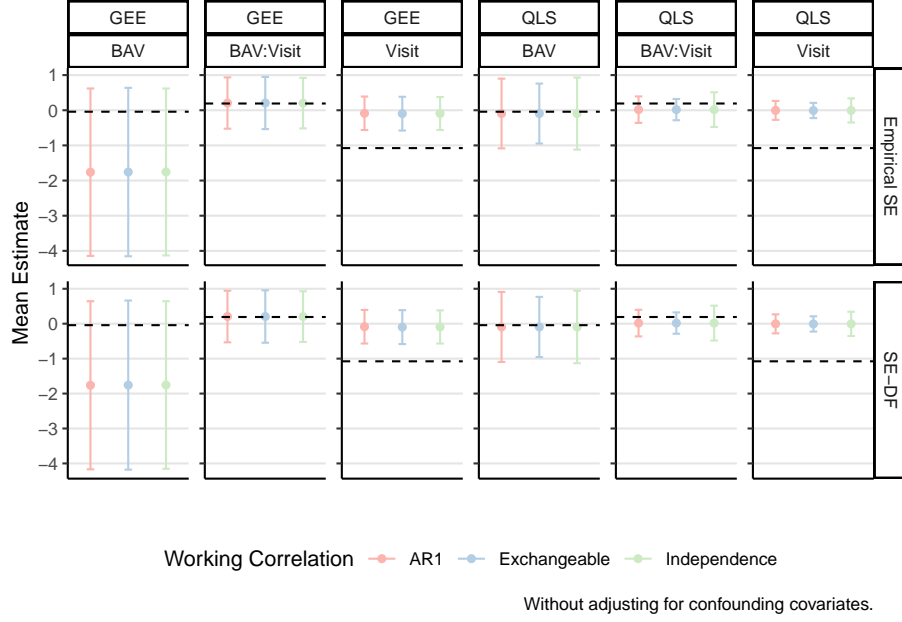


Figure 1: Comparison of Estimation Results From 1000 Simulation

Relative bias of estimates for the effect of BAV across different working correlation structures (AR1, Exchangeable, Independence) using the GEE and QLS methods, with and without including confounding covariates are presented in Figure 2. The left panel shows the GEE method, which exhibits higher variability in β_1 estimates particularly with confounding covariates, where more extreme outliers are observed. In contrast, the QLS method, shown on the right, maintains consistently low variability around zero, irrespective of the correlation structure or confounding covariate inclusion.

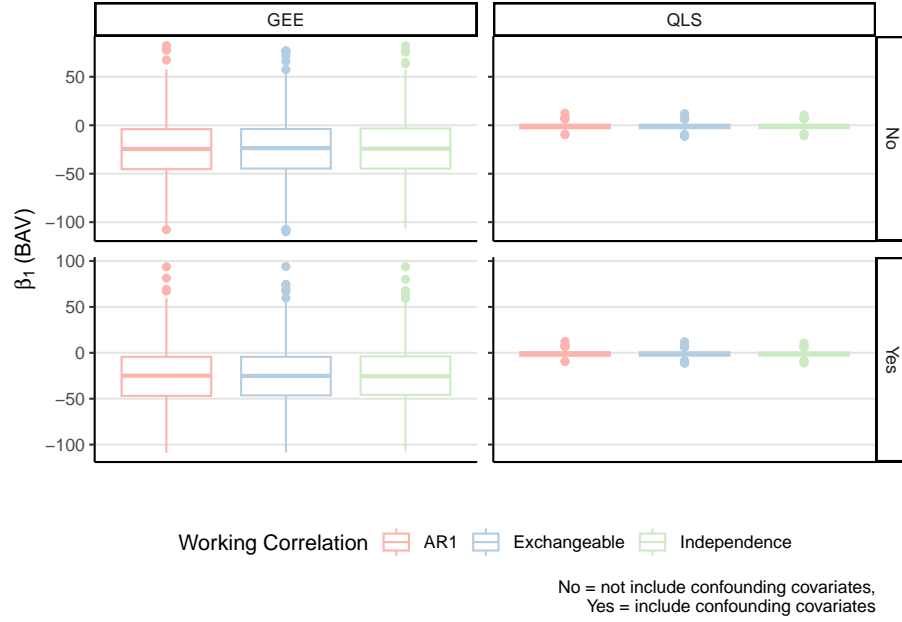


Figure 2: Relative bias of estimations for the effect of BAV using GEE and QLS with independence, AR1, and exchangeable working correlation structures.

Figure 3 shows the plot of the relative bias of estimates for the interaction effect between BAV and time. With the same layout as Figure 2, the GEE method still exhibits moderate variability with median values around zero. In contrast, the QLS method shows low variability but exhibits a negative relative bias, with estimates skewed below zero, irrespective of including confounding covariates.

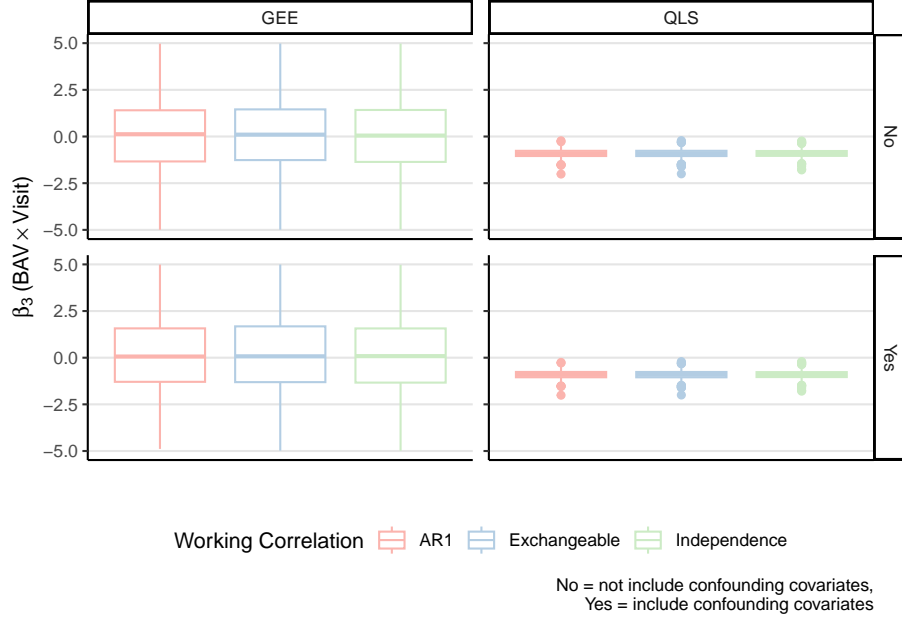


Figure 3: Relative bias of estimations for the interaction effect of BAV and time using GEE and QLS with independence, AR1, and exchangeable working correlation structures.

The comparison of the mean estimation for correlations α among longitudinal measurements between GEE and QLS methods is shown in Table 2. Given that the true intravisit correlation is set to be 0.3, the GEE method shows lower bias in the estimates of α , with a mean value of 0.166, and it shows the closest value when the specification working correlation is consistent with the true working correlation structure. However, when the working correlation is specified to be exchangeable, the GEE approach tends to underestimate the intravisit correlation at around 0.1. In contrast, the QLS method provides more consistent estimates across different covariate sets and working correlations, at around 0.7, though with generally higher bias.

Table 2: Comparison of mean estimation for the correlation among longitudinal measurements using GEE and QLS methods, with and without adjustment for age, sex, and BSA.

Working Correlation	Covariate Set	GEE		True Value	QLS	
		Mean Estimate	Bias		Mean Estimate	Bias
AR1	No	0.246	-0.054	0.3	0.727	0.427
	Yes	0.196	-0.104	0.3	0.725	0.425
Exchangeable	No	0.130	-0.170	0.3	0.561	0.261
	Yes	0.095	-0.205	0.3	0.725	0.425

* Covariate Set: Yes = Included confounding covariates, No = Without confounding covariates

Table 3 presents the estimation of correlations (τ) between subjects in matched pairs using the QLS approach, across the three different working correlations and covariate sets (with and without confounder adjustment). In general, including confounding covariates consistently have higher estimation irrespective of the specified working correlation, although the difference is ignorable. When the working correlation is specified correctly (AR1) and without including confounding covariates, the estimation are the lowest at 0.361 with a standard deviation of 0.137. With exchangeable working correlation, the mean estimation is around 0.390 with a SD of 0.111. Finally, the mean τ is estimated to be 0.486 with a SD of 0.095 when the working correlation is specified to be independence. Figure 4 visualized the estimation for τ .

Table 3: Estimation of correlations between subjects in matched pairs using QLS approach.

Working Correlation	Covariate Set	Mean τ	SD τ
AR1	No	0.361	0.137
	Yes	0.362	0.137
Exchangeable	No	0.389	0.111
	Yes	0.390	0.111
Independence	No	0.485	0.095
	Yes	0.487	0.094

* Covariate Set: Yes = Included confounding covariates, No = Without confounding covariates

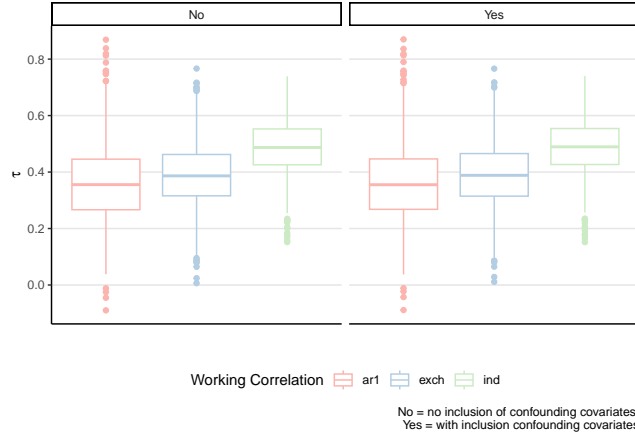


Figure 4: Estimation of intra-pair correlation using QLS approach across three different working correlation structures for both with and without inclusion of confounding covariates.

5 Discussion

In this paper, we assessed the performance and validity of the Generalized Estimating Equations (GEE) method and the two-stage quasi-least squares (QLS) approach in analyzing small matched-pair longitudinal binary data, particularly focusing on the effect of bicuspid aortic valve (BAV) on aortic root size post-surgery. We analyzed a cohort of patients from the Peter Munk Cardiac Center and performed extensive simulations to compare these methods under different working correlation structures. Our findings revealed no significant difference in performance across different specified working correlations, nor between the estimation results from the empirical sandwich estimator and the corrected ones.

In our simulation study, the QLS method demonstrates superior performance, with mean estimates closer to the true coefficients and narrower confidence intervals than GEE. Moreover, GEE tends to underestimate the intravisit correlation parameter (α) with low bias only when the working correlation is specified correctly. In contrast, QLS provided more consistent estimates of α across different working correlation specifications, although biases are much higher than those based on the GEE approach. Both methods failed to capture the effect of time. Additionally, including confounding covariates did not present large differences in performance. The findings highlight the importance of choosing an appropriate correlation structure in GEE analyses. For studies with small sample sizes and complex correlation structures, QLS may offer a more reliable alternative by providing consistent estimates with lower variability.

This study has several limitations. The small sample size of our motivational data and the assumption of AR1 as the true correlation structure may limit the generalizability of our findings. However, these limitations also present exciting opportunities for future research to explore alternative correlation structures and extend the QLS method to accommodate more complex data scenarios. The informative dropout process modeled in our simulations may not fully capture real-world complexities, but it also motivates further investigations to refine GEE and QLS approaches for handling informative dropouts and covariate endogeneity in longitudinal studies.

In conclusion, our comparative analysis of GEE and QLS methods provides valuable insights into their performance in analyzing longitudinal binary data. While GEE showed better ability to capture the correlation among repeated measurements, QLS demonstrated lower variability and consistent parameter estimates across different correlation structures. These robust findings underscore the importance of methodological considerations in longitudinal data analysis and offer confident guidance for researchers in selecting appropriate analytical approaches for their studies.

6 Appendix A

6.1 Estimation for Stage One α

Since the maximum number repeated measurement within the same subject is restricted to 6, we take $t_{ij} = 4$ as an example for simplicity. The intravisit correlation structure is

$$R_i(\alpha) = \begin{bmatrix} 1 & \alpha & \alpha^2 & \alpha^3 \\ \alpha & 1 & \alpha & \alpha^2 \\ \alpha^2 & \alpha & 1 & \alpha \\ \alpha^3 & \alpha^2 & \alpha & 1 \end{bmatrix}$$

The partial derivative of covariance matrix with respect to α is

$$\frac{\partial F_i^{-1}(\alpha)}{\partial \alpha} = \frac{\partial R_i^{-1}(\alpha)}{\partial \alpha} \otimes Q_i^{-1}(\tau)$$

because $Q_i^{-1}(\tau)$ does not contain α .

$$\frac{\partial R_i^{-1}(\alpha)}{\partial \alpha} = -R_i^{-1}(\alpha) \frac{\partial R_i(\alpha)}{\partial \alpha} R_i^{-1}(\alpha)$$

$$\frac{\partial R_i(\alpha)}{\partial \alpha} = \begin{bmatrix} 0 & 1 & 2\alpha & 3\alpha^2 \\ 1 & 0 & 1 & 2\alpha \\ 2\alpha & 1 & 0 & 1 \\ 3\alpha^2 & 2\alpha & 1 & 0 \end{bmatrix}$$

Therefore,

$$\frac{\partial R_i^{-1}(\alpha)}{\partial \alpha} = \frac{1}{(1-\alpha^2)^2} \begin{bmatrix} 2\alpha & -(1+\alpha^2) & 0 & 0 \\ -(1+\alpha^2) & 4\alpha & -(1+\alpha^2) & 0 \\ 0 & -(1+\alpha^2) & 4\alpha & -(1+\alpha^2) \\ 0 & 0 & -(1+\alpha^2) & 0 \end{bmatrix}$$

$$\frac{\partial R_i^{-1}(\alpha)}{\partial \alpha} \otimes Q_i^{-1} = \frac{1}{(1-\alpha^2)^2} \begin{bmatrix} 2\alpha Q_i^{-1} & -(1+\alpha^2)Q_i^{-1} & 0 & 0 \\ -(1+\alpha^2)Q_i^{-1} & 4\alpha Q_i^{-1} & -(1+\alpha^2)Q_i^{-1} & 0 \\ 0 & -(1+\alpha^2)Q_i^{-1} & 4\alpha Q_i^{-1} & -(1+\alpha^2)Q_i^{-1} \\ 0 & 0 & -(1+\alpha^2)Q_i^{-1} & 2\alpha Q_i^{-1} \end{bmatrix}$$

Hence,

$$\begin{aligned}
\frac{\partial Q(\beta, \Gamma)}{\partial \alpha} &= \sum_{i=1}^m \sum_{j=1}^2 (Z_{i1} \quad Z_{i2} \quad Z_{i3} \quad Z_{i4}) \frac{\partial R_i^{-1}(\alpha)}{\partial \alpha} \otimes Q_i^{-1} \begin{pmatrix} Z_{i1} \\ Z_{i2} \\ Z_{i3} \\ Z_{i4} \end{pmatrix} \\
&= \frac{1}{(1-\alpha^2)^2} \sum_{i=1}^m \sum_{j=1}^2 \left\{ 2\alpha \left(Z_{ij1} Q_i^{-1} Z_{ij1} + 2Z_{ij2} Q_i^{-1} Z_{ij2} + 2Z_{ij3} Q_i^{-1} Z_{ij3} + Z_{ij4} Q_i^{-1} Z_{ij4} \right) \right. \\
&\quad \left. 2(1+\alpha^2) \cdot \left(Z_{ij1} Q_i^{-1} Z_{ij2} + Z_{ij2} Q_i^{-1} Z_{ij3} + Z_{ij3} Q_i^{-1} Z_{ij4} \right) \right\} \\
&= \sum_{i=1}^m \sum_{j=1}^2 \left\{ \alpha \left(\sum_{k=1}^{t_{ij}} Z'_{ijk} Q_i^{-1} Z_{ijk} + \sum_{k=2}^{t_{ij}-1} Z'_{ijk} Q_i^{-1} Z_{ijk} \right) - (1+\alpha^2) \left(\sum_{k=1}^{t_{ij}-1} Z'_{ijk} Q_i^{-1} Z_{ijk+1} \right) \right\}
\end{aligned}$$

Let $S_1 = \sum_{k=1}^{t_{ij}} Z'_{ijk} Q_i^{-1} Z_{ijk} + \sum_{k=2}^{t_{ij}-1} Z'_{ijk} Q_i^{-1} Z_{ijk}$ and $S_2 = \sum_{k=1}^{t_{ij}-1} Z'_{ijk} Q_i^{-1} Z_{ijk+1}$, then

$$\begin{aligned}
\frac{\partial Q(\beta, \Gamma)}{\partial \alpha} &= \sum_{i=1}^m \sum_{j=1}^2 (\alpha S_1 - (1+\alpha^2) S_2) \\
&= \sum_{i=1}^m \sum_{j=1}^2 (\alpha S_1 - S_2 - \alpha^2 S_2) = 0 \\
&\quad \sum_{i=1}^m \sum_{j=1}^2 (\alpha^2 S_2 - \alpha S_1 + S_2) = 0 \\
\hat{\alpha}_0 &= \sum_{i=1}^m \sum_{j=1}^2 \frac{S_1 + \sqrt{S_1^2 + 4S_2^2}}{2S_2}
\end{aligned}$$

7 Appendix B

7.1 Coverage Probability

Table 4: The Coverage Probability of Regression Coefficient Estimation from GEE and QLS.

Term	GEE				QLS			
	Empirical SE	DF-SE	Empirical SE	DF-SE	Empirical SE	DF-SE	Empirical SE	DF-SE
(Intercept)	0.879	0.888	0.909	0.913	1.000	1.000	0.001	0.001
bav	0.816	0.829	0.821	0.828	1.000	1.000	1.000	1.000
bav:visit	0.861	0.865	0.861	0.863	1.000	1.000	1.000	1.000
visit	0.107	0.108	0.087	0.088	0.000	0.000	0.000	0.000
(Intercept)	0.876	0.892	0.918	0.920	0.974	0.976	0.000	0.000
bav	0.820	0.832	0.830	0.835	1.000	1.000	1.000	1.000
bav:visit	0.870	0.878	0.889	0.891	0.984	0.984	0.980	0.981
visit	0.108	0.111	0.087	0.088	0.000	0.000	0.000	0.000
(Intercept)	0.879	0.890	0.907	0.910	0.935	0.939	0.001	0.001
bav	0.811	0.823	0.821	0.823	1.000	1.000	1.000	1.000
bav:visit	0.860	0.864	0.869	0.871	0.916	0.920	0.910	0.913
visit	0.112	0.122	0.100	0.104	0.000	0.000	0.000	0.000

7.2 Simulation Results

	Corstr	Type	Term	True Value	Mean Est	SD Est	Mean SE	Mean SE-DF	Mean MSE
1	AR1	GEE	Intercept	-1.784	-2.116	4.173	2.827	2.887	17.528
3		GEE	BAV	-0.042	-1.595	7.357	1.255	1.281	56.538
4		GEE	BAV:Visit	0.192	0.149	2.163	0.390	0.398	4.682
7		GEE	Visit	-1.077	-0.019	2.138	0.256	0.261	5.691
8		QLS	Intercept	-1.784	0.128	0.315	2.012	2.055	3.755
10		QLS	BAV	-0.042	-0.093	0.117	0.509	0.520	0.016
11		QLS	BAV:Visit	0.192	0.017	0.042	0.192	0.196	0.032
14		QLS	Visit	-1.077	-0.005	0.031	0.138	0.141	1.151

Corstr: * Correlation Structure

	Corstr	Type	Term	True Value	Mean Est	SD Est	Mean SE	Mean SE-DF	Mean MSE
1	Exchangeable	GEE	Intercept	-1.784	-2.113	4.219	2.843	2.903	17.907
3		GEE	BAV	-0.042	-1.586	7.526	1.262	1.288	59.021
4		GEE	BAV:Visit	0.192	0.147	2.268	0.394	0.403	5.148
7		GEE	Visit	-1.077	-0.027	2.177	0.258	0.263	5.840
8		QLS	Intercept	-1.784	0.127	0.314	1.701	1.738	3.749
10		QLS	BAV	-0.042	-0.094	0.116	0.438	0.447	0.016
11		QLS	BAV:Visit	0.192	0.018	0.042	0.155	0.159	0.032
14		QLS	Visit	-1.077	-0.007	0.032	0.111	0.114	1.146

Corstr: * Correlation Structure

	Corstr	Type	Term	True Value	Mean Est	SD Est	Mean SE	Mean SE-DF	Mean MSE
1		GEE	Intercept	-1.784	-2.062	4.207	2.823	2.883	17.778
3		GEE	BAV	-0.042	-1.583	7.450	1.255	1.281	57.873
4	Independence	GEE	BAV:Visit	0.192	0.145	2.209	0.385	0.393	4.882
7		GEE	Visit	-1.077	-0.023	2.174	0.253	0.259	5.837
8		QLS	Intercept	-1.784	0.131	0.318	2.753	2.812	3.769
10		QLS	BAV	-0.042	-0.094	0.114	0.524	0.535	0.016
11		QLS	BAV:Visit	0.192	0.017	0.039	0.246	0.251	0.032
14		QLS	Visit	-1.077	-0.005	0.029	0.172	0.175	1.150

Corstr, SD, MSE: * Correlation Structure, Standard Deviation and Mean Squared Error

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