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Simulation-based study comparing multiple imputation methods for non-monotone missing ordinal data in longitudinal settings

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Abstract

The application of multiple imputation (MI) techniques as a preliminary step to handle missing values in data analysis is well established. The MI methods can be classified into two broad classes, the joint modeling and the fully conditional specification approaches. Their relative performance for longitudinal ordinal data setting is not well documented. This paper intends to fill this gap by conducting a large simulation study on the estimation of the parameters of a longitudinal proportional odds model. The two MI methods are also illustrated on a real dataset of quality of life in a cancer clinical trial.

Keywords: ordinal variables; longitudinal analysis; non-monotone; intermittent; missing at random; multiple imputation

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1 Introduction

In clinical trials, it is common practice to assess quality of life (QoL) on a Likert-type scale along with the patient's disease evolution [1]. Patients however may withdraw prematurely from the trial or miss one or more follow-up visits. The latter situation refers to intermittent or non-monotone missingness pattern and the former to monotone missingness. The statistical analysis of non-Gaussian longitudinal data with non-monotone missingness pattern is difficult to handle. Even when the number of patients with intermittent missing data is small, discarding these patients from the analysis [2] is unsatisfactory and alternative methods have to be considered.

Multiple imputation (MI) has become a reference method for handling missing data [3]. For longitudinal ordinal data with monotone missingness patterns, MI consists in a sequential application of the proportional odds model considering the previous assessment time as covariate and accounting for the uncertainty about the regression coefficients [4]. We shall refer to this method as the ordinal imputation model (OIM). Even if inappropriate for ordinal data, it is common practice to impute ordinal data using a MI approach for continuous data based on multivariate normality [5]. This MI method will be refereed to as multivariate Normal imputation (MNI). In a previous work of our group, we compared the performance of both approaches for the monotone setting and we clearly demonstrates the superiority of the OIM approach [6]. The OIM method however hardly works for non-monotone missing data and it has been suggested to apply the MNI method based on multivariate normality [5] even if inappropriate for ordinal data. Here, we propose to adapt the OIM method to longitudinal ordinal data with non-monotone missingness patterns.

Multivariate MI methods can be classified into two broad classes, respectively the joint modeling (JM) and the fully conditional specification (FCS). The latter is also known as chained equation, variable-by-variable imputation or regression switching. Within the JM approach, the joint distribution of the data has to be specified (e.g. normality). The idea of the FCS imputation method is to bypass the definition of the joint distribution by specifying a conditional distribution for each variable where data need to be imputed. In the subsequent, we shall assume that covariates are fully observed and only the ordinal outcome can be missing. Thus, a proportional odds model needs to be specified at each assessment time point.

We shall adapt the FCS strategy to monotone and non-monotone missing ordinal data by means of widely available statistical software procedures. The performance of the proposed method was compared to the joint modeling that assume a multivariate normal distribution method by focusing on the estimation of the parameters of a longitudinal proportional odds model. Both imputation methods were assessed through Monte Carlo simulated artificial data sets and also illustrated on a real example. The simulations will cover well-balanced outcome data but also skewed distributions, as often observed in QoL studies.

The paper is organized as follows. The proportional odds model to analyze longitudinal ordinal data is briefly reviewed in Section 2, while a general overview of the problem of missing data is given in Section 3. Section 4 outlines the theoretical background of multiple imputation including those for continuous and ordinal variables. The simulation experimental design is described in Section 5 and results are presented in Section 6. Both MI methods are illustrated on a QoL dataset in Section 7. Concluding remarks are given in Section 8.

2 The QoL dataset

The QoL data used in this work were obtained from the EORTC phase III clinical trial 26981 comparing radiotherapy (RT) and radiotherapy plus concomitant daily temozolomide, followed by adjuvant temozolomide (RT+TMZ) in patients with newly diagnosed and histologically confirmed glioblastoma. Between August 2000 and March 2002, a total of 573 patients were randomized by 85 institutions in 15 countries in this trial, respectively 286 in the RT arm and 287 in the RT+TMZ arm. Clinical and QoL results have been published previously [7, 8].

Per protocol, QoL had to be assessed in all patients using the EORTC QLQ-C30 version 2 questionnaire [9]. In the RT arm, QoL assessment was performed at baseline (ie, before start of treatment), during radiotherapy at 4 weeks, 4 weeks after completion of the radiotherapy and then every three months until disease progression. In the RT+TMZ arm, QoL assessment was performed at baseline, during radiotherapy and concomitant chemotherapy at week 4, 4 weeks after RT at the end of the third and sixth cycle of adjuvant temozolomide, and then every 3 months until disease progression. At the time of the analysis, time windows for acceptable QoL forms were defined around each time point to gather the maximum information available [8]. Since there were only a few assessments available after the first two follow-up time points, the analysis was stopped there.

In this paper, we shall consider the appetite loss (AP) scale of the QLQ-C30 as the outcome varaible. AP is an ordinal variable with 4 response categories ('Not at all', 'A little', 'Quite a bit', 'Very much'). Since only few patients reported category 'Very much', the two last categories were combined into a single one. In the following, the time of AP assessment was treated as a categorical covariate. The distributions of AP according to time points and treatment groups are displayed in Table 1.

Table 1: Distribution of appetite loss (Number (%)) for each time point and treatment arm

	RT arm			RT+TMZ arm		
Time	Not at all	A little	Quite a bit Very much	Not at all	A little	Quite a bit Very much
T0 - Baseline	201 (81.4)	35 (14.2)	11 (4.45)	206 (85.5)	21 (8.71)	14 (5.81)
T1 - During RT	148 (78.7)	28 (14.9)	12 (6.38)	133 (66.2)	41 (20.4)	27 (13.4)
T2 - After RT	104 (73.2)	27 (19.0)	11 (7.75)	109 (66.1)	39 (23.6)	17 (10.3)
T3 - FU1	45 (73.8)	13 (21.3)	3 (4.92)	58 (62.4)	22 (23.7)	13 (14.0)
T4 - FU2	25 (80.7)	4 (12.9)	2 (6.45)	61 (75.3)	17 (21.0)	3 (3.70)

FU1 = first follow-up / FU2 = second follow-up

In cancer trials, the drop-out is typically linked to disease progression and death. Furthermore, it has been shown that no sharp increase or decrease was observed in scores just before missingness, which is usually a good indicator for non-ignorable missing data [7, 8]. A total of 29 different missingness patterns was observed for AP. The distribution of the complete, monotone and non-monotone missingness patterns in each treatment group is summarized in Table 2.

Table 2: Distribution of the different missingness patterns (Number (%)) in both treatment arms

Missingness pattern	RT arm	RT+TMZ arm
Complete	15 (5.62)	30 (11.2)
Monotone	200 (74.9)	138 (51.3)
Non-monotone	52 (19.5)	101 (37.6)
Total	267	269

3 Models for longitudinal ordinal data

3.1 The proportional odds model

Consider a sample of N subjects and let Y be an ordered variable with K categories assessed on T occasions in each subject. Then, let Y_{ij} denote the assessment of the ordinal variable Y for the ith subject ($i = 1, ..., N$) at the jth occasion ($j = 1, ..., T$). Hence, $\mathbf{Y}_i =$

$(Y_{i1}, ..., Y_{iT})'$ is the vector of the repeated assessments of the ith subject and $\mathbf{Y}_j = (Y_{1j}, ..., Y_{Nj})'$ is the vector of responses at the jth occasion. Associated with each subject, there is a $p \times 1$ vector of covariates, say $\mathbf{x}_{ij}$, measured at time j. Hence, let $\mathbf{X}_i = (\mathbf{x}_{i1}, ..., \mathbf{x}_{iT})'$ denote the $T \times p$ design matrix of the ith subject. Covariates typically include time of measurement, age, gender, treatment group, and so on.

The ordinal nature of the outcome variable may be accounted for by considering the cumulative probabilities $Pr(Y_{ij} \leq k), k = 1, \cdots, K$. The cumulative proportional odds model is a popular choice to relate the marginal probabilities of Y to the covariate vector $\mathbf{x}$ [10]. Specifically,

$$\text{logit}[\Pr(Y_{ij} \leq k|\mathbf{x}_{ij})] = \beta_{0k} + \mathbf{x}_{ij}'\boldsymbol{\beta} \tag{1}$$

where $\boldsymbol{\beta_0} = (\beta_{01}, ..., \beta_{0,K-1})'$ is the vector of the intercept parameters and $\boldsymbol{\beta} = (\beta_1, ..., \beta_p)'$ the vector of coefficients ($i = 1, ..., N$; $j = 1, ..., T$; $k = 1, ..., K-1$). Under the proportional odds assumption, $\boldsymbol{\beta}$ does not depend on k.

3.2 Generalized estimating equations

Estimation of the regression coefficients of marginal models can be approached by likelihood-based or non-likelihood-based methods. One difficulty present with likelihood models resides in the complexity of the relationship between the parameters of the model and the joint probabilities that define the likelihood. Alternative solutions to likelihood-based analysis have been explored, in particular the generalized estimating equations (GEE), quite popular for the analysis of non-Gaussian correlated data. This approach circumvents the specification of the joint distribution of the repeated responses by means of a ‘working’ correlation matrix and only the marginal distributions are specified. Since the proportional odds model is not part of the regular generalized linear model family, some transformations are required before applying the GEE method. Following Lipsitz *et al.* [11], a $(K-1)$-dimensional expanded vector of binary responses has to be created for each subject at each occasion, $\mathbf{Y}_{ij}^{*} = (Y_{i1j}^{*}, ..., Y_{i,(K-1),j}^{*})'$ where $Y_{ikj}^{*} = 1$ if $Y_{ij} = k$ and 0 otherwise. Now,

$$\text{logit}[\Pr(Y_{ij} \leq k|\mathbf{x}_{ij})] = \text{logit}[\Pr(Y_{ikj}^{*} = 1|\mathbf{x}_{ij})], \ \ k = 1, ..., K-1 \tag{2}$$

Since the logistic regression model is a member of the generalized linear model family, the GEE method applies and consistent estimates of the regression parameters can be obtained by solving the estimating equations

$$\sum_{i=1}^{N} \frac{\partial \boldsymbol{\pi}_i'}{\partial \boldsymbol{\beta}} \mathbf{V}_i^{-1}(\mathbf{Y}_i^{*} - \boldsymbol{\pi}_i) = \mathbf{0} \tag{3}$$

where $\mathbf{Y}_i^{*} = (\mathbf{Y}_{i1}^{*}, ..., \mathbf{Y}_{iT}^{*})'$, $\boldsymbol{\pi}_i = E(\mathbf{Y}_i^{*})$, $\mathbf{V}_i = \mathbf{A}_i^{1/2}\mathbf{R}_i\mathbf{A}_i^{1/2}$ with $\mathbf{A}_i$ the diagonal matrix of the variance of the elements of $\mathbf{Y}_i^{*}$, and $\boldsymbol{\beta}$ the expanded vector of intercepts and regression coefficients. The matrix $\mathbf{R}_i$ is the 'working' correlation matrix that expresses the dependence among repeated observations over the subjects ranging from independence to exchangeable, banded, or unstructured.

4 Missingness

In line with the notation introduced previously, consider the missing data indicators, R_{ij}, defined as follows:

$$R_{ij} = \begin{cases} 1 \text{ if } Y_{ij} \text{ is observed,} \\ 0 \text{ otherwise,} \end{cases}$$

and let $\boldsymbol{R}_i = (R_{i1}, \ldots, R_{iT})'$ the indicator vector corresponding to $\mathbf{Y}_i = (Y_{i1}, \ldots, Y_{iT})'$.

Now $\mathbf{Y}_i$ can be split into two subvectors $(\mathbf{Y}_i^o, \mathbf{Y}_i^m)$ where $\mathbf{Y}_i^o$ refers to the observed component of $\mathbf{Y}_i$ and $\mathbf{Y}_i^m$ refers to the missing component part.

When missing data occur, we are concerned with the distribution of the measurement process together with the missing-data process. Little and Rubin [12, 13, 14] identified two broad classes of joint models: the selection model and the pattern-mixture model. In the selection model, the joint distribution $(\mathbf{Y}_i, \boldsymbol{R}_i)$ is split into the marginal distribution of the measurement and the distribution of the missingness process conditional on the measurement $\mathbf{Y}_i$. By contrast, the pattern-mixture model specifies the marginal distribution of $\boldsymbol{R}_i$ and the conditional distribution of $\mathbf{Y}_i$ given $\boldsymbol{R}_i$. Here we shall focus on the selection model approach in which Rubin [4] and Little and Rubin [12] made essential distinctions between the processes responsible for the missingness: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). The determination of the mechanism responsible for missing data has a decisive implication on the choice of the statistical method used to analyze the data. Under the MCAR mechanism, the probability of an observation being missing is independent of both $\mathbf{Y}^o$ and $\mathbf{Y}^m$. Under the MAR mechanism, the probability of an observation being missing is independent of $\mathbf{Y}^m$ given $\mathbf{Y}^o$. When neither MCAR nor MAR holds, the missingness mechanism is said to be MNAR, whence the probability of an observation being missing depends on $\mathbf{Y}^m$.

Liang and Zeger [15] pointed out that GEE are only valid under the restrictive assumption that the data are missing completely at random (MCAR). Alternative methods were investigated to allow the analysis of data under less strict missingness assumptions. Robins *et al.* [16, 17] developed an extension of the GEE, known as the weighted generalized estimating equations (WGEE), that provide consistent estimates of the regression parameters even under the MAR assumption. With their method, each subject's measurements is weighted in the GEE by the inverse probability of dropping out at that time point. Another alternative to analyze the data under the MAR assumption is multiple imputation based on GEE (MI-GEE). In this approach, missing values are imputed several times [4, 18] and the resulting completed datasets are analyzed using standard GEE methods. Using Rubin's rules, the final results obtained from the completed datasets are combined into a single inference. In the context of longitudinal binary data, Beunckens *et al.* [19] showed by simulations that, in spite of the asymptotic unbiasedness of WGEE, the combination of GEE and multiple imputation is both less biased and more accurate in small to moderate sample sizes which typically arise in clinical trials. In this paper, focus will be on MI-GEE methods.

5 Multiple imputation

5.1 Theoretical framework

The idea behind multiple imputation is to replace each missing value wit a set of $M > 1$ plausible values drawn from the conditional distribution of the missing data given the observed data. This conditional distribution represents the uncertainty about the right value to impute in the sense that the set of M imputed values properly represents the information about the missing value that is contained in the observed data.

Using the notation introduced in previous sections, let $\boldsymbol{\theta}$ represents the parameter vector of the distribution of the response $\mathbf{Y}_i = (\mathbf{Y}_i^o, \mathbf{Y}_i^m)$. Note that $\boldsymbol{\theta}$ may differ from the parameters $\boldsymbol{\beta}$ of the substantive model. The observed data $\mathbf{Y}^o$ will be used to estimate the conditional distribution of $\mathbf{Y}^m$ given $\mathbf{Y}^o$, $f(\mathbf{Y}^m|\mathbf{Y}^o, \boldsymbol{\theta})$. If $\boldsymbol{\theta}$ is known, the values for $\mathbf{Y}^m$

can be drawn from $f(\mathbf{Y}^m|\mathbf{Y}^o,\boldsymbol{\theta})$. For $\boldsymbol{\theta}$ unknown, an estimate is obtained from the data, say $\hat{\boldsymbol{\theta}}$; then missing values will be imputed using $f(\mathbf{Y}^m|\mathbf{Y}^o,\hat{\boldsymbol{\theta}})$. Frequentists incorporate uncertainty in $\boldsymbol{\theta}$ by using bootstrap or other methods. A Bayesian prior distribution for $\boldsymbol{\theta}$ can also be chosen. Given this distribution, a draw $\boldsymbol{\theta}^*$ is generated and now values for $\mathbf{Y}^m$ can be drawn from $f(\mathbf{Y}^m|\mathbf{Y}^o,\boldsymbol{\theta}^*)$. These two steps for the construction of the imputed data are the first phase of MI. Then the substantive model is applied to each of the M completed data $(\mathbf{Y}_i^o,\mathbf{Y}_i^{m*})$. Let $\hat{\boldsymbol{\beta}}_{\boldsymbol{m}}$ and $\hat{\boldsymbol{U}}_m$ be the vector of estimates and the corresponding variance-covariance matrix for the m^{th} imputed data set $(m = 1,\ldots,M)$, respectively. The last step of MI is the combination of the M results. The MI point estimate for $\boldsymbol{\beta}$ is simply the average of the M complete-data point estimates [4, 5],

$$\hat{\boldsymbol{\beta}}^* = \frac{1}{M}\sum_{m=1}^{M}\hat{\boldsymbol{\beta}}_m$$

A measure of the precision of $\hat{\boldsymbol{\beta}}^{\boldsymbol{*}}$ is obtained by Rubin's variance formula [4] which combines the within- and the between-imputation variability. Define $\mathbf{W}$, the within-imputation variance, as the average of the M within imputation variance estimates $\hat{\boldsymbol{U}}_m$,

$$\mathbf{W} = \frac{1}{M}\sum_{m=1}^{M}\hat{\boldsymbol{U}}_m$$

and $\mathbf{B}$, the between-imputation variance, measuring the variability across the imputed values,

$$\mathbf{B} = \frac{1}{M-1}\sum_{m=1}^{M}(\hat{\boldsymbol{\beta}}_m - \hat{\boldsymbol{\beta}}^*)(\hat{\boldsymbol{\beta}}_m - \hat{\boldsymbol{\beta}}^*)'$$

Then, the variance estimate associated with $\hat{\boldsymbol{\beta}}^*$ is the total variance

$$\mathbf{T} = \mathbf{W} + \left(1 + \frac{1}{M}\right)\mathbf{B}$$

where $\left(1+\frac{1}{M}\right)$ is a correction factor for the finite number of imputations.

5.2 MNI method

In Bayesian inference, information about unknown parameters is expressed in the form of posterior probability distributions computed using Bayes' theorem. In this context, Markov Chain Monte Carlo methods (MCMC) have been considered to explore and simulate the entire joint posterior distribution of the unknown quantities through the use of Markov chains.

Assuming that data arise from a multivariate normal distribution, Schafer [5] developed a method based on an MCMC process for generating proper imputations that accounts for between imputation variability, the MNI approach. This approach, based on the algorithm of data augmentation [20], is a procedure that iterates between an imputation step (I-step) and a posterior step (P-step). In the I-step, given starting values for the mean and the covariance matrix, i.e. given starting values for $\boldsymbol{\theta}$, values for missing data $\mathbf{Y}^m$ are simulated by randomly drawing a value from the conditional multivariate normal distribution of $\mathbf{Y}^m$ given $\mathbf{Y}^o$, $f(\mathbf{Y}^m|\mathbf{Y}^o, \boldsymbol{\theta})$. After the first iteration, new values for $\boldsymbol{\theta}$ are drawn from its posterior distribution. Both steps are iterated, which creates a Markov chain $(\mathbf{Y}^m_{(1)}, \boldsymbol{\theta}_{(1)}), (\mathbf{Y}^m_{(2)}, \boldsymbol{\theta}_{(2)}), \cdots$ where each step depends on the previous one, introducing dependency across the steps. The two steps are then iterated long enough until the distribution becomes stationary. Imputations from the last iteration are used to impute the missing values of the dataset. More detail about this procedure can be found in [5].

When proceeding this way for an ordinal outcome, the imputed values obtained are no longer integer values and need then to be rounded off to the nearest integer (category) or to the nearest plausible value. However, in the binary case, it was demonstrated that rounding is not recommended because the rounded imputed values may provide biased parameter estimates [21, 22, 23]. In situations like ours, where one is concerned with missing values for the outcome variable, unrounded values are physically not plausible. So, the rounding phase is unavoidable before application of the substantive model (e.g. GEE with proportional odds model).

5.3 FCS based on ordinal imputation model

The adaptation of the ordinal imputation model (OIM) to arbitrary missingness pattern appears as an alternative to the MNI approach. To impute missing data for an ordinal outcome, one has to impose a probability model on the complete data. In the presence of an ordinal outcome variable, a proportional odds model will be considered to link the ordinal outcome to a set of q covariates. The FCS with an ordinal imputation model is based on the Gibbs sampling algorithm; that is random draws from the multivariate distribution of interest, $f(\mathbf{Y}^m|\mathbf{Y}^o, \boldsymbol{\theta})$, is be obtained by iteratively drawing from the conditional distribution of each outcome assessment. This imputation process is composed of two steps, a filled-in step and an imputation step.

Filled-in step

In this step, all missing value, $\mathbf{Y}^m$, are filled-in using an arbitrary method. Let $\mathbf{Y}^{(0)} = (\mathbf{Y}_1^{(0)}, \cdots, \mathbf{Y}_T^{(0)})$ where $\mathbf{Y}_j^{(0)} = (\mathbf{Y}_j^o, \mathbf{Y}_{j*}^{(0)})$ with $\mathbf{Y}_j^o$ the observed part of the jth assessment of the ordinal outcome Y and $\mathbf{Y}_{j*}^{(0)}$ its filled-in part. $\mathbf{Y}^{(0)}$ will serve as initial starting values for the imputation step.

Imputation step

In this second step, the previously filled-in elements of $\mathbf{Y}_{j*}^{(0)}$ are imputed using the specified conditional distribution, $f(\mathbf{Y}_j^m|\mathbf{Y}_j^o, \boldsymbol{\theta}_j)$. These imputations are made in turn for all $\mathbf{Y}_j^m$

$(j = 1, \cdots, T)$. In order to obtain imputed values that are independent of the starting values, $\mathbf{Y}^{(0)}$, the cycling imputation through all $\mathbf{Y}_j^m$ $(j = 1, \cdots, T)$ is repeated several times. The imputations above will be based on the following proportional odds model,

$$logit[Pr(Y_{ij}^m \leq k)|\mathbf{x}_{ij}^*] \quad = \quad \theta_{jk} + \mathbf{x'}_{ij}^*\boldsymbol{\theta_{xj}}, \tag{4}$$

where the covariates typically include those of the substantive model $\boldsymbol{X}_{ij}$, possible auxiliary covariates $\boldsymbol{A}_{ij}$, and the other outcomes $\mathbf{Y}_{-j} = (\mathbf{Y}_1, \cdots, \mathbf{Y}_{(j-1)}, \mathbf{Y}_{(j+1)}, \cdots, \mathbf{Y}_T)$. To realize proper imputation [4], uncertainty about $\boldsymbol{\theta}_j = (\theta_{jk}, \boldsymbol{\theta}_{xj})$ has to be accounted for. For this purpose, a value for $\boldsymbol{\theta}_j$ is drawn from an appropriate posterior distribution about $\boldsymbol{\theta}_j$ conditionally on the most recently imputed data. One way of proceeding is known as the "Normal approximation draw" method. This method is correct for linear regression [4] but is near far a reasonable approximation for situation involving categorical regression. Nevertheless, it is a common practice, supported by the law of large-sample, to use this Normal approximation [4]. To correct for possible misleading association that could have been introduced in the filled-in step, the proportional odds model is fitted on the part of the dataset with observed observation for the jth assessment, $\mathbf{Y}_j^o$, which might contain observations with imputed values for the other assessments, $\mathbf{Y}_{-j}$.

Based on these considerations, the tth iteration of the imputation step goes as follows,

$\mathbf{Y}_1^{(t)}$: 1. Fit the proportional odds model (4) on the part of the dataset for which $\mathbf{Y}_1$ is fully observed and draw new values for $\hat{\boldsymbol{\theta}}_1$ using

$$\boldsymbol{\theta}_{1*} = \hat{\boldsymbol{\theta}}_1 + \boldsymbol{V}'_{hi}\mathbf{Z},$$

where $\boldsymbol{V}'_{hi}$ is the upper triangular matrix of the Cholesky decomposition, $\boldsymbol{V}_i = \boldsymbol{V}'_{hi}\boldsymbol{V}_{hi}$ of the covariance matrix of $\hat{\boldsymbol{\theta}}_1$ and $\mathbf{Z}$ is a $(K-1)+q$ vector of independent random normal variates.

2. For each element of $\mathbf{Y}_1^m$ compute

   $P[Y_{i1}^m = k|\boldsymbol{\theta}_{1*}, \mathbf{Y}_1^o, \mathbf{Y}_2^{(t-1)}, \cdots, \mathbf{Y}_T^{(t-1)}, \mathbf{x}_{i1}, \boldsymbol{A}_{i1}]$ from equation (4).

3. For each element of $\mathbf{Y}_1^m$ draw a random variate from a multinomial distribution with probabilities derived in step 2.

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$\mathbf{Y}_T^{(t)}$:

1. Fit the proportional odds model (4) on the part of the dataset for which $\mathbf{Y}_T$ is fully observed and draw new values for $\hat{\boldsymbol{\theta}}_T$ using

$$\boldsymbol{\theta}_{T*} = \hat{\boldsymbol{\theta}}_T + \boldsymbol{V}'_{hi}\mathbf{Z},$$

   where $\boldsymbol{V}'_{hi}$ is the upper triangular matrix of the Cholesky decomposition, $\boldsymbol{V}_i = \boldsymbol{V}'_{hi}\boldsymbol{V}_{hi}$ of the covariance matrix of $\hat{\boldsymbol{\theta}}_T$ and $\mathbf{Z}$ is a $(K-1)+q$ vector of independent random normal variates.

2. For each element of $\mathbf{Y}_T^m$ compute $P[Y_{iT}^m = k|\boldsymbol{\theta}_{T*}, \mathbf{Y}_1^t, \mathbf{Y}_2^{(t)}, \cdots, \mathbf{Y}_T^o, \mathbf{x}_{i1}, \boldsymbol{A}_{i1}]$ from equation (4).

3. For each element of $\mathbf{Y}_T^m$ draw a random variate from a multinomial distribution with probabilities derived in step 2.

The previous cyclic iteration process is repeated several times, usually between 10-20 [25, 24], until stabilization of the results. As within the Gibbs sampling algorithm, convergence is influenced by the choice of the initial values, $\mathbf{Y}^{(0)}$. In the filled-in step, we then replace the missing values using an ordinal logistic regression sequentially by order of assessment.

6 SIMULATION STUDY

To assess the performance of both imputation methods (MNI and FCS OIM), we conducted a large simulation study as described hereafter.

6.1 Longitudinal ordinal data-generating model

Correlated ordinal responses were generated with the SAS macro developed by Ibrahim [26] and based on Lee's algorithm [27]. The basic measurement model utilized in this study includes as covariates a binary group effect ($X = 0$ or 1), an assessment time (T) and an interaction term between group and time, so that the proportional odds model (Eq. 1) is written as:

$$\text{logit}[\Pr(Y_{ij} \leq k | x_i, t_j)] = \beta_{0k} + \beta_x x_i + \beta_t t_j + \beta_{tx} x_i t_j. \tag{5}$$

($i = 1, \cdots, N$; $j = 1, \cdots, T$; $k = 1, \cdots, K-1$). An exchangeable correlation structure was considered.

6.2 Missing data generating mechanisms

The mechanism used to generate MAR missingness data is based on the following binary logistic regression model:

$$\text{logit}[\Pr(R_{ij} = 0 | x_i, Y_{i,(j-1)})] = \psi_0 + \psi_x x_i + \psi_{prev} Y_{i,(j-1)} \tag{6}$$

($i = 1, \cdots, N$; $j = 1, \cdots, T$; $k = 1, \cdots, K-1$). Thus, the probability to be missing at a certain time point j depends on the binary covariate X and the outcome value at the previous time point $Y_{i,(j-1)}$.

6.3 Simulation patterns

Theoretical values of the model parameters (see (Eq. 5)) considered in our simulations are given in Table 3 for a well-balanced and skewed distribution.

Table 3: Values of the model parameters used for generating longitudinal ordinal dataset (well-balanced and skewed distribution)

Distribution	K	β_{01}	β_{02}	β_{03}	β_{04}	β_{05}	β_{06}	β_x	β_t	β_{tx}
Well-balanced										
	2	-0.25	-	-	-	-	-	0.10	0.10	-0.15
	3	-0.71	0.66	-	-	-	-	0.10	0.10	-0.15
	4	-1.10	0.00	1.10	-	-	-	0.10	0.10	-0.15
	5	-1.39	-0.41	0.41	1.39	-	-	0.10	0.10	-0.15
	7	-1.79	-0.92	-0.29	0.29	0.92	1.79	0.10	0.10	-0.15
Skewed										
	2	1.00	-	-	-	-	-	0.80	0.10	-0.25
	3	-2.20	-0.85	-	-	-	-	0.80	0.10	-0.25
	4	-0.41	0.00	0.41	-	-	-	0.80	0.10	-0.25
	5	-0.85	-0.20	0.20	0.85	-	-	0.80	0.10	-0.25
	7	-1.39	-0.66	-0.16	0.16	0.66	1.39	0.80	0.10	-0.25

Three distinct sample sizes N were considered for the simulation: 100, 300 and 500, equally distributed between both groups. This covers small (50 subjects/arm) to large studies (250 subjects/arm). For the assessment time points T, two possibilities were envisaged corresponding to short ($T = 3$) or long ($T = 5$) longitudinal study. Note that for skewed data, only $T = 3$ was considered. The ordinal outcome variable Y covered several numbers of categories $K = 2, 3, 4, 5$ and 7, respectively. Finally, the population parameters of (Eq. 6) ($\psi_0, \psi_x, \psi_{prev}$) were chosen to yield a rate of missingness approximatively equal to 10%, 30% and 50%, respectively. The complete data case (0% missingness) was also considered. Thus, both imputation methods were assessed on 90 different combination patterns. For each pattern, S = 500 random samples were generated. The two MI methods (MNI and FCS OIM) were applied to impute missing data on the same incomplete dataset allowing a paired comparaison of the two approaches. A GEE model was then fitted to the resulting multiply imputed datasets. For each MI method, the number of multiple imputation was fixed to $M = 20$ [4, 28]. As the generation of the MAR missingness was based on the binary covariate X, the latter had to be included in the imputation model. In the GEE model, the same working correlation matrix as the one used in the generation data process was considered, that is an exchangeable correlation matrix. The MI based on MNI and on FCS OIM were carried out using the SAS MI procedure. The GEE SAS macro based on the extension of Lipsitz *et al.* method [11] and implemented by Williamson *et al.* [29] was used to analyze the imputed datasets. Finally, the SAS MIANALYZE procedure was used to pool the results obtained.

6.4 Evaluation criteria

For each simulation pattern, the relative bias $RB = \hat{\beta}/\beta$ expressed in percent was averaged over the $S = 500$ replicated datasets. Likewise, the mean square error was calculated as

$$MSE = Bias^2 + Var(\hat{\beta})$$

with $Var(\hat{\beta}) = \sum_{s=1}^{S} \frac{(\hat{\beta}_s - \bar{\hat{\beta}})^2}{(S-1)}$, $\bar{\hat{\beta}} = \sum_{s=1}^{S} \frac{\hat{\beta}_s}{S}$ and $Bias = \bar{\hat{\beta}} - \beta$.

The effect of the modeling parameters on RB was assessed by multiple regression analysis and so was the difference between RB obtained by MNI and FCS OIM, respectively. To account for the matching between both imputation methods, a generalized linear mixed model taking all modeling parameters as covariates was applied to the MSE derived after imputation. This statistical scheme was applied to both kinds of generated ordinal data, well-balanced and skewed distribution.

7 Results

The values of the relative bias (%) and the MSE calculated over the 500 replicate samples are detailed in Appendices for both imputation methods. For clarity, results for intercepts were omitted.

7.1 Well-balanced distributions

Relative bias

Table 4 reports the mean (±SD) of RB of each regression parameter derived under both imputation methods as well as their differences. Globally, underestimated values of the model parameters were found using the MNI method, while estimates derived with the FCS OIM method were almost unbiased. Although differences between the two imputation methods were highly significant ($p < 0.0001$) for all regression parameters, the RB difference was small ($3 - 8\%$).

When considering the results under the various simulation patterns, the following observations could be made. For the binary effect parameter, β_x, using the MNI method, the RB was unchanged for K and rate of missingness but it varied according to the number of time points ($p = 0.001$) and to N ($p = 0.019$). In fact, RB was lower in short term than in long term studies (92.9 ± 15.9 % vs 101.8 ± 10.5 %; $p = 0.001$) and it decreased from 100.1 ± 18.8 % for N=100 to 92.1 ± 9.27 % for $N = 500$. Nearly the same conclusions apllied for the RB derived under the FCS OIM process. The RB remained unchanged with T and the rate of missingness but decraesed with K ($p = 0.009$) and with N ($p = 0.022$). The RB for the time effect parameter, β_t, and for the interaction term, β_{tx}, behaved similarly under both MI methods. It significantly decreased with K ($p < 0.0001$), the rate of missingness ($p < 0.05$) and increased with the number of time point ($p < 0.05$) but was unchanged for N. Overall, for each simulation pattern, better RB values were obtained under the FCS OIM approach.

Table 4: Relative bias (mean ± SD) of the parameters of the substantive model after imputation of the ordinal outcome using MNI and FCS OIM methods.

Globally and according to the modeling parameters

		β_x			β_t			β_{tx}		
		MNI	FCS OIM	Diff	MNI	FCS OIM	Diff	MNI	FCS OIM	Diff
Global		97.4 ± 14.1	100.1 ± 12.7	-2.78 ± 3.92	90.4 ± 14.1	98.3 ± 9.22	-7.90 ± 6.34	95.2 ± 6.09	99.2 ± 4.57	-4.02 ± 2.53
				< 0.0001			< 0.0001			< 0.0001
K	2	93.7 ± 13.6	99.1 ± 12.0	-5.36 ± 3.84	99.0 ± 4.87	102.4 ± 6.31	-3.40 ± 2.27	96.4 ± 3.71	100.1 ± 2.65	-3.70 ± 2.65
	3	110.5 ± 12.9	111.7 ± 12.9	-1.12 ± 1.75	97.1 ± 6.30	102.4 ± 4.71	-5.34 ± 2.44	99.6 ± 5.48	102.9 ± 4.77	-3.30 ± 1.63
	4	93.9 ± 14.4	98.0 ± 12.0	-4.05 ± 4.69	88.0 ± 11.2	97.6 ± 4.91	-9.58 ± 6.75	94.4 ± 7.10	99.2 ± 4.82	-4.80 ± 3.29
	5	95.5 ± 10.8	97.5 ± 12.1	-2.01 ± 2.20	90.5 ± 8.55	100.3 ± 4.99	-9.86 ± 6.56	93.3 ± 4.75	97.5 ± 3.00	-4.14 ± 2.53
	7	93.2 ± 11.8	94.6 ± 7.68	-1.35 ± 4.63	77.5 ± 21.7	88.8 ± 14.1	-11.3 ± 7.92	92.3 ± 6.46	96.4 ± 4.52	-4.16 ± 2.31
		0.086	0.009	0.003	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.063
T	3	92.9 ± 15.9	97.8 ± 14.3	-4.89 ± 3.86	85.4 ± 18.1	96.7 ± 12.6	-11.3 ± 7.01	92.4 ± 7.09	97.8 ± 5.75	-5.34 ± 2.61
	5	101.8 ± 10.5	102.5 ± 10.6	-0.66 ± 2.65	95.4 ± 4.72	99.9 ± 3.01	-4.51 ± 2.93	98.0 ± 3.02	100.7 ± 2.22	-2.70 ± 1.61
		0.001	0.064	<0.001	<0.0001	0.046	<0.0001	<0.0001	0.0005	<0.0001
N	100	100.1 ± 18.8	102.4 ± 17.2	-2.27 ± 3.97	92.1 ± 14.7	99.5 ± 10.1	-7.36 ± 6.17	96.0 ± 7.77	99.6 ± 6.39	-3.58 ± 2.40
	300	99.9 ± 11.4	102.9 ± 10.4	-2.94 ± 4.01	90.4 ± 14.4	98.4 ± 9.32	-7.99 ± 6.50	95.7 ± 5.32	99.9 ± 3.50	-4.17 ± 2.60
	500	92.1 ± 9.27	95.2 ± 7.57	-3.12 ± 3.87	88.6 ± 13.4	97.0 ± 8.37	-8.35 ± 6.53	93.9 ± 4.73	98.2 ± 3.04	-4.30 ± 2.61
		0.019	0.022	0.29	0.15	0.20	0.23	0.043	0.16	0.013
Missingness	10	100.1 ± 1.6	101.9 ± 13.4	-1.74 ± 1.32	97.3 ± 6.76	100.8 ± 5.55	-3.51 ± 2.66	98.7 ± 4.31	100.4 ± 4.06	-1.71 ± 0.87
	30	97.9 ± 14.7	100.8 ± 13.1	-2.95 ± 3.75	90.9 ± 11.4	99.4 ± 7.41	-8.54 ± 5.86	95.6 ± 5.62	99.7 ± 4.58	-4.18 ± 1.90
	50	94.1 ± 13.9	97.8 ± 11.6	-3.64 ± 5.43	83.1 ± 18.2	94.7 ± 12.4	-11.7 ± 6.86	91.4 ± 5.99	97.5 ± 4.69	-6.17 ± 2.23
		0.074	0.18	0.020	<0.0001	0.003	<0.0001	<0.0001	0.0045	<0.0001

Mean square error

The mean square error (mean $\pm$ SD) of each regression parameters under both imputation methods and their difference are given in Table 5. Globally, although results were significant, difference between MNI and FCS OIM were minute and not practically relevant. From this perspective, MNI and FCS OIM were similar.

As expected, under both imputation methods and for each model parameter, the MSE decreased significantly (p $<$ 0.0001) with the sample size N. A decrease was also observed with T ($p < 0.0001$). The number of categories K and rate of missingness did not affect MSE.

Table 5: Mean square error (mean ± SD) of the parameters of the substantive model after imputation of the ordinal outcome using MNI and OIM methods.

Globally and according to the modeling parameters

		β_x			β_t			β_{tx}		
		MNI	FCS OIM	Diff	MNI	FCS OIM	Diff	MNI	FCS OIM	Diff
Global		0.120 ± 0.101	0.117 ± 0.098	0.003 ± 0.007	0.010 ± 0.011	0.010 ± 0.011	-0.000 ± 0.001	0.019 ± 0.021	0.019 ± 0.022	-0.000 ± 0.001
				< 0.0001			0.008			0.038
K	2	0.139 ± 0.119	0.141 ± 0.121	-0.002 ± 0.002	0.011 ± 0.013	0.012 ± 0.013	-0.001 ± 0.001	0.022 ± 0.025	0.023 ± 0.026	-0.001 ± 0.002
	3	0.116 ± 0.100	0.113 ± 0.096	0.002 ± 0.005	0.010 ± 0.011	0.010 ± 0.012	-0.000 ± 0.001	0.019 ± 0.022	0.020 ± 0.022	-0.000 ± 0.000
	4	0.122 ± 0.108	0.117 ± 0.102	0.005 ± 0.007	0.010 ± 0.012	0.010 ± 0.012	-0.000 ± 0.001	0.020 ± 0.024	0.020 ± 0.024	-0.000 ± 0.000
	5	0.112 ± 0.096	0.108 ± 0.091	0.005 ± 0.007	0.009 ± 0.010	0.009 ± 0.011	-0.000 ± 0.000	0.017 ± 0.019	0.017 ± 0.019	0.000 ± 0.000
	7	0.111 ± 0.089	0.105 ± 0.081	0.007 ± 0.010	0.011 ± 0.012	0.010 ± 0.011	0.000 ± 0.001	0.017 ± 0.018	0.017 ± 0.018	0.000 ± 0.001
		0.12	0.031	<0.0001	0.65	0.36	<0.0001	0.16	0.09	<0.0001
T	3	0.160 ± 0.118	0.154 ± 0.115	0.006 ± 0.009	0.017 ± 0.012	0.018 ± 0.013	-0.000 ± 0.001	0.032 ± 0.024	0.032 ± 0.024	-0.000 ± 0.001
	5	0.081 ± 0.058	0.080 ± 0.058	0.001 ± 0.003	0.003 ± 0.002	0.003 ± 0.002	-0.000 ± 0.000	0.006 ± 0.004	0.006 ± 0.005	-0.000 ± 0.000
		<0.0001	<0.0001	0.0001	<0.0001	<0.0001	0.016	<0.0001	<0.0001	0.038
N	100	0.240 ± 0.087	0.233 ± 0.084	0.007 ± 0.011	0.020 ± 0.014	0.021 ± 0.015	-0.0001 ± 0.001	0.038 ± 0.027	0.038 ± 0.028	-0.000 ± 0.001
	300	0.075 ± 0.025	0.074 ± 0.024	0.002 ± 0.003	0.007 ± 0.005	0.007 ± 0.005	-0.000 ± 0.000	0.012 ± 0.008	0.012 ± 0.008	-0.000 ± 0.000
	500	0.045 ± 0.015	0.044 ± 0.015	0.001 ± 0.002	0.004 ± 0.003	0.004 ± 0.003	0.000 ± 0.000	0.007 ± 0.005	0.007 ± 0.005	-0.000 ± 0.000
		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	0.16
Missingness	10	0.116 ± 0.100	0.115 ± 0.099	0.001 ± 0.002	0.009 ± 0.011	0.009 ± 0.011	-0.000 ± 0.000	0.018 ± 0.021	0.018 ± 0.021	-0.000 ± 0.000
	30	0.120 ± 0.101	0.117 ± 0.099	0.003 ± 0.005	0.010 ± 0.011	0.010 ± 0.011	-0.000 ± 0.001	0.019 ± 0.021	0.019 ± 0.021	-0.000 ± 0.001
	50	0.125 ± 0.105	0.119 ± 0.098	0.006 ± 0.011	0.011 ± 0.012	0.012 ± 0.013	-0.000 ± 0.001	0.020 ± 0.023	0.021 ± 0.023	-0.000 ± 0.001
		0.46	0.73	0.0008	0.18	0.13	0.040	0.44	0.40	0.15

7.2 Skewed distributions

As mentioned in the simulation plan, the impact of both imputation methods within the skewed ordinal data setting has been investigated in the context of a short term study, that is $T = 3$. Simulation results are summarized in the Appendices.

The overall RBs under both imputation methods are depicted in Figure 1 for each regression parameter. Globally, the MNI method overestimated the binary and the interaction term parameters of the model, while at the same time underestimated the time parameter β_t. As in the well-balanced setting, the OIM method yielded less biased estimates. The median RB difference between the two imputation methods ranged from 2% to 10%, with the worst results observed for the time parameter, β_t. In fact, the lowest RB value of β_t was equal to 52.6% and the highest RB value was equal to 205.6%; both extremes values were obtained under the MNI method. The extreme RBs under the OIM method presented the same but less marked behaviour; they were equal to 76.7% and 144.4%, respectively.

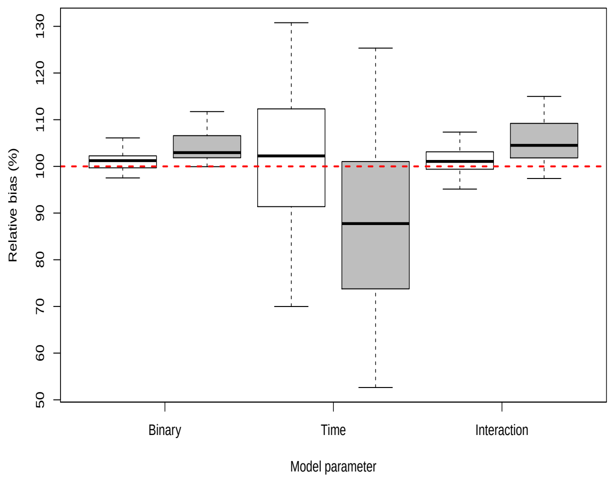

Figure 1: Global Relative bias (%) of the model parameters (β_x, β_t, β_{tx}) (MNI= shaded boxplot - OIM=empty boxplot)

The effect of the modeling parameters on the RB derived under both imputation methods was found to be the same for K and N but not for the rate of missingness. As shown in Figure 2, under both multiple imputation methods, the RB varied according to K, especially for the time effect. While no association was found between RB and the rate of missingness for the OIM, Figure 3 shows that, except for the time effect, RB under MNI increased significantly with the rate of missingness (β_x: $p = 0.0003$, β_t: $p = 0.99$, β_{tx}: $p < 0.0001$). No relationship was observed between the RBs derived under both MI methods and the sample size, N.

The MSE of each regression parameter under both imputation methods and their differences are displayed in Table 6. Comparison of the MSE calculated in presence of skewed ordinal outcomes with those derived in well-balanced setting showed that MSE values were larger in presence of skewness. Contrary to the well-balanced setting, differences in the behaviors of the MSE were observed with respect to the modeling parameters, especially according to K.

As expected, under both imputation methods and for each model parameter, the MSE decreased significantly (p < 0.0001) with the sample size N. Contrary to the well-balanced setting, MSE values got lower as the number of categories K increased. However, these falls in the MSE behaved differently in the two MI methods for the binary and the interaction terms of the model. For the binary effect of the model, the difference in MSE increased with the number of categories of the ordinal outcome ($p < 0.0001$), while for the interaction term the MSE difference decreased ($p < 0.0001$). While the rate of missingness did not affect MSE; the difference in MSE between the two MI methods increased with the rate of missingness.

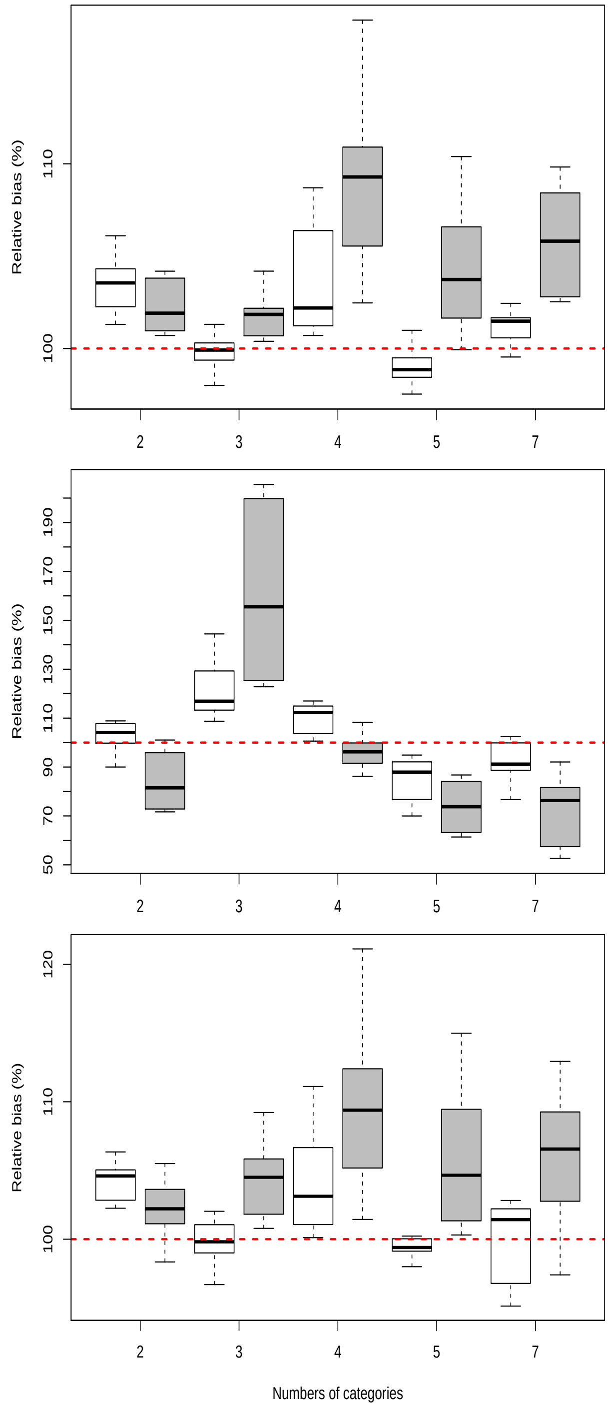

Figure 2: Relative bias (%) of the model parameters (β_x, β_t, β_{tx}) according to K the number of categories of the ordinal outcome (MNI= shaded boxplot - OIM=empty boxplot)

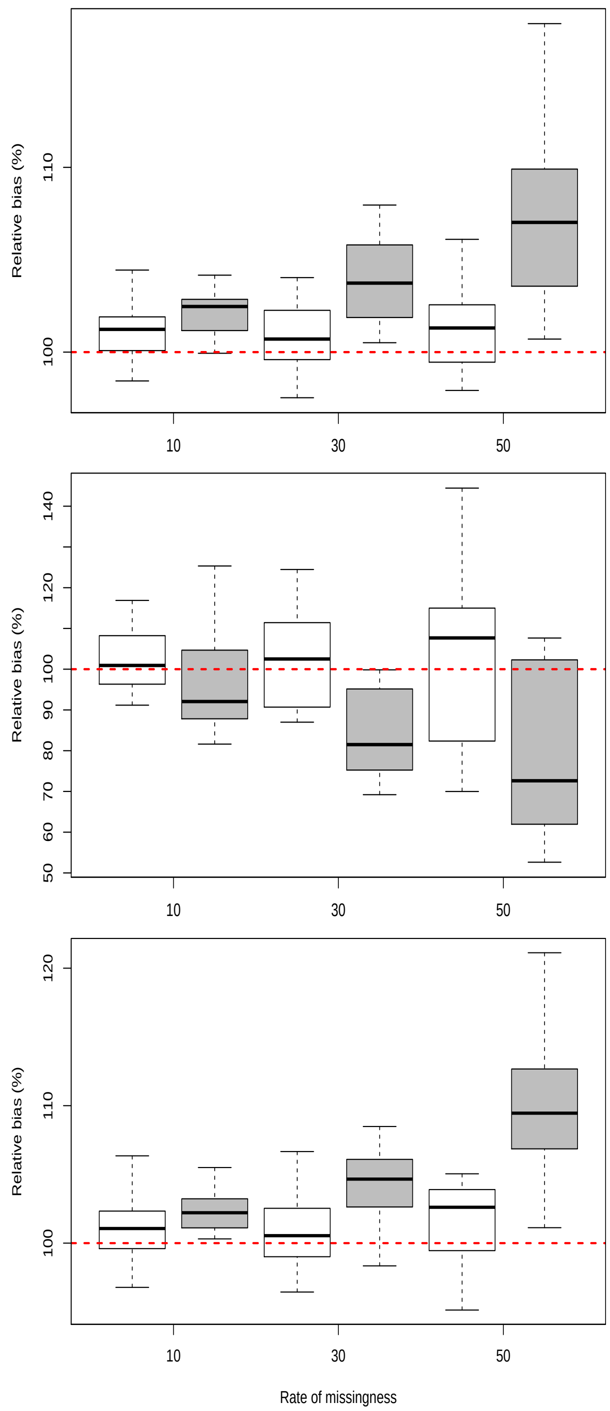

Figure 3: Relative bias (%) of the model parameters (β_x, β_t, β_{tx}) according to the rate of missingness (MNI= shaded boxplot - OIM=empty boxplot)

Table 6: Mean square error (mean ± SD) of the parameters of the substantive model after imputation of the ordinal outcome using MNI and OIM methods, globally and according to the modeling parameters (skewed distribution)

		β_x			β_t			β_{tx}		
		MNI	FCS OIM	Diff	MNI	FCS OIM	Diff	MNI	FCS OIM	Diff
Global		0.203 ± 0.170	0.198 ± 0.172	0.005 ± 0.013	0.021 ± 0.017	0.021 ± 0.017	0.000 ± 0.002	0.041 ± 0.035	0.042 ± 0.037	-0.001 ± 0.003
				< 0.0001			0.84			< 0.0001
K	2	0.339 ± 0.264	0.350 ± 0.271	-0.011 ± 0.011	0.034 ± 0.026	0.035 ± 0.026	-0.001 ± 0.001	0.070 ± 0.054	0.075 ± 0.057	-0.005 ± 0.005
	3	0.180 ± 0.132	0.179 ± 0.131	0.001 ± 0.002	0.024 ± 0.015	0.021 ± 0.014	0.003 ± 0.004	0.036 ± 0.026	0.038 ± 0.028	-0.002 ± 0.002
	4	0.165 ± 0.119	0.153 ± 0.111	0.012 ± 0.011	0.016 ± 0.012	0.017 ± 0.013	-0.001 ± 0.001	0.032 ± 0.025	0.033 ± 0.025	-0.001 ± 0.001
	5	0.174 ± 0.135	0.165 ± 0.129	0.008 ± 0.008	0.017 ± 0.013	0.017 ± 0.014	-0.000 ± 0.001	0.034 ± 0.027	0.035 ± 0.027	-0.001 ± 0.001
	7	0.159 ± 0.115	0.145 ± 0.104	0.014 ± 0.015	0.015 ± 0.011	0.015 ± 0.011	0.000 ± 0.001	0.030 ± 0.023	0.030 ± 0.023	0.000 ± 0.001
		0.0015	0.0005	< 0.0001	< 0.0001	0.0001	0.87	0.0007	0.0003	< 0.0001
N	100	0.404 ± 0.148	0.395 ± 0.164	0.009 ± 0.021	0.041 ± 0.015	0.041 ± 0.015	-0.000 ± 0.003	0.081 ± 0.032	0.084 ± 0.035	-0.003 ± 0.004
	300	0.130 ± 0.044	0.127 ± 0.050	0.003 ± 0.008	0.014 ± 0.005	0.013 ± 0.005	0.000 ± 0.002	0.026 ± 0.010	0.027 ± 0.012	-0.001 ± 0.002
	500	0.076 ± 0.022	0.074 ± 0.026	0.002 ± 0.005	0.009 ± 0.004	0.008 ± 0.003	0.001 ± 0.002	0.015 ± 0.006	0.016 ± 0.007	-0.001 ± 0.001
		< 0.0001	< 0.0001	0.070	< 0.0001	< 0.0001	0.23	< 0.0001	< 0.0001	0.007
Missingness	10	0.196 ± 0.171	0.194 ± 0.172	0.002 ± 0.004	0.019 ± 0.015	0.019 ± 0.016	-0.000 ± 0.000	0.039 ± 0.034	0.039 ± 0.035	-0.000 ± 0.001
	30	0.201 ± 0.171	0.196 ± 0.173	0.005 ± 0.010	0.021 ± 0.017	0.021 ± 0.017	0.000 ± 0.001	0.040 ± 0.035	0.041 ± 0.036	-0.002 ± 0.002
	50	0.213 ± 0.179	0.205 ± 0.184	0.008 ± 0.021	0.024 ± 0.019	0.023 ± 0.020	0.001 ± 0.004	0.043 ± 0.038	0.046 ± 0.041	-0.003 ± 0.004
		0.62	0.77	0.094	0.11	0.19	0.32	0.50	0.36	0.007

8 QoL data EXAMPLE

We applied both imputation methods on the QoL data (see Table 7).

Table 7: Results of the MI-GEE (proportional odds model) when using MNI and FCS OIM as multiple imputation method

Parameter	MNI		FCS - OIM	
	Estimate (SE)	P-value	Estimate (SE)	P-value
β_{01}	1.41 (0.17)	< 0.0001	1.46 (0.15)	< 0.0001
β_{02}	3.59 (0.21)	< 0.0001	2.94 (0.21)	< 0.0001
T_1	-0.36 (0.22)	0.11	-0.097 (0.20)	0.62
T_2	-0.73 (0.22)	0.001	-0.52 (0.22)	0.021
T_3	-0.92 (0.24)	0.0001	-0.43 (0.33)	0.20
T_4	-0.70 (0.35)	0.054	0.10 (0.36)	0.77
$TRT \times T_0$	0.21 (0.27)	0.44	0.26 (0.26)	0.32
$TRT \times T_1$	-0.52 (0.22)	0.017	-0.69 (0.23)	0.003
$TRT \times T_2$	-0.12 (0.22)	0.59	-0.23 (0.23)	0.32
$TRT \times T_3$	-0.26 (0.26)	0.32	-0.47 (0.37)	0.21
$TRT \times T_4$	0.01 (0.34)	0.97	-0.47 (0.42)	0.27

TRT is treatment (0 = RT, 1 = RT+TMZ); T0 = Baseline; T1 = During RT; T2 = After RT; T3 = FU1; T4 = FU2

Results derived under the MNI method showed that AP was more severe during RT (p = 0.001) and after RT (p = 0.0001) than at baseline. Moreover, severe AP affected more RT + TMZ patients than RT patients ($TRT \times T_1$; p = 0.017) during treatment. When applying the FCS OIM approach, the time effect disappeared except after RT (p = 0.021). As for the MNI approach, the deleterious effect was significantly higher in RT + TMZ patients (p = 0.0003). The difference between the two MI methods is evidenced in Figure 4 where the probabilities of each category at each assessment time in both treatment arms are displayed for both MI approaches.

Increasing the number of imputations up to 100 to test the robustness of the results did not change the conclusions.

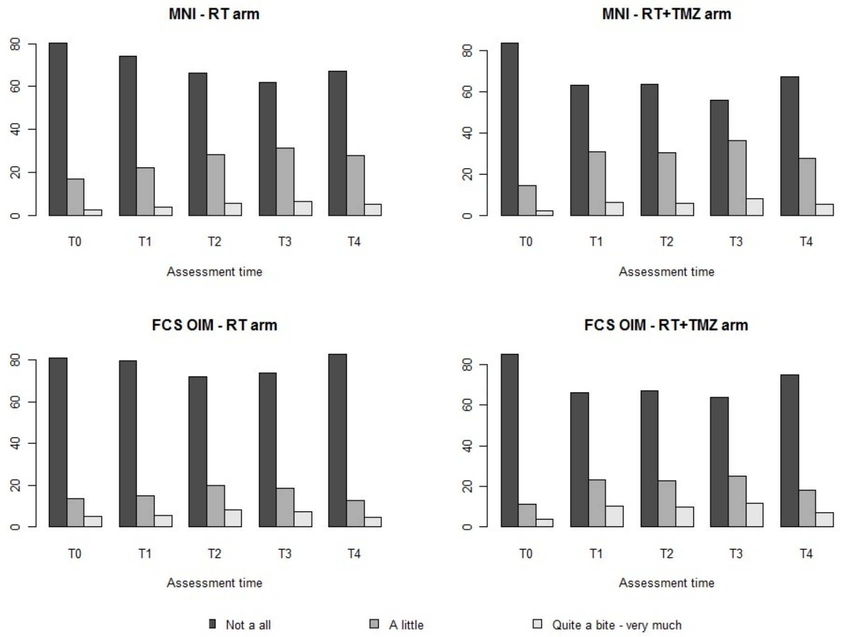

Figure 4: Distribution of appetite loss at each assessment time and in each treatment arm for both MI methods

9 DISCUSSION

Several studies have compared MNI and FCS imputation methods [25, 31, 30] but to the best of our knowledge, none have focused on longitudinal ordinal outcome data. This study was designed to compare the performance of the two methods, available in most statistical packages, in the context of longitudinal ordinal datasets with non-monotone missing values. The comparison was based on a comprehensive simulation plan covering a wide range of real life situations. Specifically, the parameters of the experimental design included the following parameters: number of categories of the ordinal outcome (K), number of time points (T), sample size (N) and rate of missingness (%) but also the form of the distribution (well-balanced or skewed) of the ordinal outcome data. Both MI methods were also applied on a real QoL dataset. The performance of the two MI methods was appraised by the relative bias and the mean square error of the regression parameters of the model. The latter included a group effect and a time effect, as well as their interaction.

Within the well-balanced setting, the model parameters were slightly underestimated in the MNI approach as compared to the FCS OIM method which yielded almost unbiased estimates. Except for the binary term where effects were less marked, both imputation methods behaved similarly for each regression parameters. Under both MI methods, RB decreased with K and the rate of missingness, increased with the number of assessment time and was unchanged for the sample size (N). However, within each simulation pattern, RB values derived under the FCS OIM were slightly better than those derived under the MNI process. For all regression parameters, the MSE of both imputation methods were comparable.

For skewed data, application of the MNI process led to a marked overestimation of the regression coefficients of the binary and the interaction terms and an underestimation of the time coefficient. Overall, estimates derived under FCS OIM process were less biased. While, RB evolved differently according to K under both MI methods, it was only affected by the rate of missingness under MNI. In both distribution settings, estimation of the time effect coefficient was more biased than the other coefficients.

Although globally, simulations did not evidenced a large differences between the performance of the two MI methods, some simulation patterns were clearly against MNI. This was confirmed by the AP dataset where the ordinal outcome had K=3 categories, a skewed distribution and a large amount of missing data. Application of the two MI methods led to different conclusions, in particular for the time effect.

Within the longitudinal setting, Donneau *et al.* [6] previously showed that the OIM method provides less biased results when imputing drop out cases than the MNI method. In comparison with those findings where the RB difference between the two imputation methods ranged from 9% to 16%, the difference between the MNI and the FCS OIM method found here was much lower (3% to 8%). As far as the MSE is concerned, the conclusions made for the non-monotone setting paralleled those found for the monotone setting.

Based on the results of this large simulation study and application to QoL dataset, salient conclusions may be drawn. Although theoretically unsuitable for ordinal data, the MNI method with rounding imputation to the nearest integer value globally provided better acceptable results than expected. However, as shown across the different simulation patterns, some situations were less favorable for MNI than for FCS OIM. This remark was reinforced by results of the QoL dataset where different conclusions applied according to the MI method used. Finally, as for the analysis model, the choice of the imputation method should be guided by the type of the data that needs to be imputed. Thus, it is advisable to impute missing ordinal data using suitable MI method.

References

1. Olschewski, M., Schulgen, G., Schumacher, M. and Altman, D.G. Quality of life assessment in clinical cancer research. *British journal of cancer* 1994. **70**: 1–5.

2. Carpenter, J.R., Kenward, M. G. Missing data in randomised controlled trials a practical guide Birmingham: National Institute for Health Research 2007. Available at *www.missingdata.org.uk*.**1–206**.

3. Rubin, D. Multiple imputation in sample surveys - a phenomenological bayesian

approach to nonresponse. *Imputation and Editing of Faulty or Missing Survey Data* 1978. **1–32**.

4. Rubin, D. B. *Multiple imputations for nonresponse in survey* . Wiley: New York, 1987.

5. Schafer, J. L. Multiple imputation for Nonresponse in Survey *Chapman & Hall*1997

6. Donneau, A.F., Mauer, M., Molenberghs, G. and Albert, A. A simulation study comparing multiple imputation methods for incomplete longitudinal ordinal data. 2012 **submitted**

7. Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine* 2005; **352**(10):987–996.

8. Taphoorn MJ, Stupp R, Coens C et al. Health-related quality of life in patients with glioblastoma: a randomized controlled trial. *Lancet Oncology* 2005; **6**(12):937–944.

9. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman DB, De Haes JCJM, Kaasa S, Klee M, Osoba D, Razavi D, Rofe P, Schraub S, Sneeuw K, Sullivan M, Takeda F. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85**:365–376.

10. McCullagh, P. Regression models for ordinal data (with discussion). *Journal of the Royal Statistical Society, Series B* 1980; **42**:109–142.

11. Lipsitz, SR., Kim, K., Zhao, L. Analysis of repeated categorical data using generalized estimating equations. *Statistics in Medicine* 1994; **13**(11):1149–1163.

12. Little, R. J. A., Rubin, D. B. *Statistical Analysis with Missing Data* . Wiley: New York, 1987.

13. Little, R. J. A. Pattern-mixture models for multivariate incomplete data. *Journal of the American Statistical Association* 1993. **88**:125–134.

14. Little, R. J. A. Modeling the drop-out mechanism in repeated measures studies. *Journal of the American Statistical Association* 1995. **90**:1112–1121.

15. Liang, K.-Y., Zeger, S. L. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; **73**:13–22.

16. Robins, J. M., Rotnitzky, A. Semiparametric efficiency in multivariate regression models with missing data. *Journal of the American Statistical Association* 1995; **90**:122–129.

17. Robins, J. M., Rotnitzky, A., Zhao, L. Analysis of semiparametric regression models with missing data. *Journal of the American Statistical Association* 1995; **90**:106–121.

18. Rubin, D. B. Inference and missing data. *Biometrika* 1976; **63**:581–592.

19. Beunckens, C., Sotto, C., Molenberghs, G. A simulation study comparing weighted estimating equations with multiple imputation based estimating equations for longitudinal binary data. *Computational Statistics and Data Analysis* 2008; **52**:1533–1548.

20. Tanner, M. A., Wong, W. H. The calculation of posterior distribution by data augmentation *Journal of American Statistical Association* 1987, **82**: 528–550.

21. Horton, N., Lipsitz, S., Parzen, M. A potential for bias when rounding in multiple imputation *The American Statistician* 2003, **57**:229–232.

22. Ake, C. Rounding after multiple imputation with non-binary categorical covariates. *Paper presented at SAS Users Group international* 2005. *Thirty annual conference,Philadelphia.*

23. Allison, P. Imputation of categorical variables with PROC MI *Paper presented at SAS Users Group international* 2005. *Thirty annual conference,Philadelphia*

24. White, Ian R. and Royston, Patrick and Wood, Angela M. Multiple imputation using chained equations: Issues and guidance for practice *Statistics in Medicine*2011, **30**(4):377–399.

25. van Buuren, S. Multiple imputation of discrete and continuous data by full conditional specification *Statistical Methods in Medical Research*2007 **16**:219–242.

26. Ibrahim, N., Suliadi, S. Generating correlated discrete ordinal data using R and SAS IML *Computer Methods and Programs in Biomedicine* 2011; **104**(3):122–132.

27. Lee, A. J. Some simple methods for generating correlated categorical variates *Computational Statistics and Data Analysis* 1997; **26**:133–148.

28. Graham, J. W., Olchowski, A. E., Gilreath, T. D. How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory *Prevention Science* 2007; **8**:206-213.

29. Williamson, J., Lipsitz, S., Kim, K. GEECAT and GEEGOR: computer programs for the analysis of correlated categorical response data. *Computer Methods and Programs in Biomedicine* 1999; **58**:25–34 .

30. Lee, K. and Carlin, J. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation *American Journal of Epidemiology* 2012 **71**:624–632.

31. Demirtas, H., Freels, S. and Yucel R. Plausibility of multivariate normality assumption when multiply imputing non-Gaussian continuous outcomes: a simulation assessment. *Journal of Statistical Computation and Simulation* 2008 **78**:69–84.

10 Appendices

Table 8: Simulation results for the MI-GEE based MNI and OIM methods (K = 2 - Well-balanced distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			87.7	0.389	90.1	0.393	88.7	0.372	95.2	0.376	83.9	0.360	97.0	0.366
		β_t			104.2	0.037	106.0	0.038	107.0	0.037	111.9	0.040	109.4	0.039	116.6	0.043
		β_{tx}			96.9	0.075	98.5	0.076	98.0	0.073	102.4	0.075	93.2	0.074	102.6	0.081
3	300	β_x			93.8	0.104	95.9	0.104	89.7	0.102	96.5	0.103	88.3	0.103	99.1	0.107
		β_t			99.1	0.012	100.4	0.012	99.2	0.012	103.2	0.013	105.6	0.012	111.8	0.013
		β_{tx}			98.2	0.021	99.8	0.021	95.5	0.021	100.4	0.022	93.2	0.021	100.9	0.024
3	500	β_x			75.5	0.071	79.1	0.071	72.9	0.066	79.9	0.067	72.0	0.067	84.4	0.068
		β_t			94.8	0.007	96.6	0.008	94.1	0.007	98.1	0.008	102.6	0.008	110.9	0.009
		β_{tx}			92.3	0.015	95.2	0.015	90.1	0.014	94.6	0.014	89.4	0.015	98.1	0.016
5	100	β_x			112.6	0.186	113.7	0.187	118.4	0.195	119.8	0.196	113.5	0.195	120.5	0.201
		β_t			97.5	0.007	98.1	0.007	98.7	0.008	100.7	0.008	97.7	0.008	101.3	0.009
		β_{tx}			101.6	0.016	102.2	0.016	103.0	0.016	105.1	0.016	99.8	0.017	103.6	0.017
5	300	β_x			105.1	0.063	106.3	0.63	102.8	0.063	105.5	0.065	103.4	0.064	110.6	0.067
		β_t			97.6	0.002	98.4	0.003	96.9	0.003	99.1	0.003	95.6	0.003	100.3	0.003
		β_{tx}			99.7	0.005	100.6	0.005	98.1	0.005	100.2	0.005	96.8	0.005	101.2	0.006
5	500	β_x			96.4	0.035	98.0	0.036	93.0	0.035	96.2	0.035	88.9	0.035	95.5	0.037
		β_t			96.3	0.001	97.3	0.001	94.5	0.001	96.8	0.001	91.5	0.001	95.8	0.001
		β_{tx}			98.4	0.003	99.4	0.003	96.9	0.003	99.2	0.003	93.9	0.003	98.5	0.003

Table 9: Simulation results for the MI-GEE based on MNI and OIM methods (K = 3 - Well-balanced distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			137.2	0.298	140.8	0.296	131.0	0.315	131.0	0.307	118.6	0.327	115.8	0.308
		β_t			108.5	0.031	112.8	0.032	100.9	0.032	107.5	0.033	89.8	0.036	96.5	0.038
		β_{tx}			112.3	0.062	114.9	0.063	109.4	0.064	113.0	0.065	99.1	0.068	103.6	0.070
3	300	β_x			112.9	0.091	115.2	0.090	104.1	0.096	106.7	0.093	102.1	0.097	100.8	0.093
		β_t			101.9	0.010	106.1	0.010	93.3	0.011	102.3	0.011	88.8	0.011	96.3	0.012
		β_{tx}			104.2	0.019	106.3	0.019	98.1	0.020	103.2	0.021	95.0	0.021	100.3	0.022
3	500	β_x			97.4	0.053	99.4	0.052	99.6	0.054	100.7	0.053	92.6	0.058	92.9	0.055
		β_t			95.9	0.006	100.2	0.006	91.0	0.007	99.6	0.007	86.3	0.007	94.6	0.008
		β_{tx}			97.3	0.011	99.3	0.011	95.8	0.012	99.2	0.012	89.5	0.012	95.6	0.013
5	100	β_x			122.0	0.147	122.5	0.146	117.9	0.150	116.7	0.150	118.4	0.154	120.0	0.152
		β_t			105.4	0.007	106.6	0.007	102.9	0.007	106.8	0.007	98.5	0.007	104.7	0.007
		β_{tx}			103.6	0.011	104.4	0.011	101.0	0.012	103.1	0.012	98.7	0.012	102.6	0.012
5	300	β_x			115.1	0.049	115.4	0.049	114.0	0.049	117.1	0.049	116.4	0.050	118.3	0.051
		β_t			103.5	0.002	105.0	0.002	100.0	0.002	104.1	0.002	94.6	0.002	101.0	0.002
		β_{tx}			102.3	0.004	103.2	0.004	100.2	0.004	103.0	0.004	98.0	0.004	102.5	0.004
5	500	β_x			98.9	0.030	99.8	0.030	97.9	0.031	99.6	0.030	93.6	0.031	97.1	0.031
		β_t			99.6	0.001	101.2	0.001	96.0	0.001	100.3	0.001	90.2	0.001	97.5	0.001
		β_{tx}			99.2	0.003	100.2	0.003	97.0	0.003	99.7	0.003	93.1	0.003	98.1	0.003

Table 10: Simulation results for the MI-GEE based on MNI and OIM methods (K = 4 - Well-balanced distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			73.6	0.318	77.7	0.312	63.0	0.332	70.8	0.317	67.0	0.368	72.9	0.340
		β_t			98.9	0.031	105.0	0.030	83.4	0.032	98.1	0.032	72.2	0.039	91.0	0.042
		β_{tx}			90.5	0.064	93.2	0.064	82.7	0.066	89.0	0.065	79.8	0.079	88.3	0.079
3	300	β_x			93.2	0.098	96.6	0.097	92.5	0.109	101.1	0.104	84.9	0.119	98.1	0.111
		β_t			91.7	0.008	98.0	0.008	80.6	0.010	96.3	0.010	66.9	0.012	89.1	0.012
		β_{tx}			95.3	0.018	98.0	0.018	93.2	0.020	100.7	0.020	85.0	0.024	96.3	0.024
3	500	β_x			100.3	0.057	104.4	0.056	94.2	0.059	103.5	0.057	81.4	0.067	95.1	0.063
		β_t			92.9	0.006	99.7	0.006	81.4	0.006	97.9	0.006	64.3	0.008	85.5	0.008
		β_{tx}			99.1	0.011	1022	0.011	93.4	0.012	101.3	0.012	85.3	0.014	96.6	0.015
5	100	β_x			107.0	0.138	106.3	0.137	107.9	0.146	108.8	0.143	103.8	0.146	103.6	0.141
		β_t			100.9	0.006	102.4	0.006	97.9	0.006	102.7	0.006	90.1	0.006	98.0	0.007
		β_{tx}			103.4	0.011	104.3	0.011	102.1	0.011	104.5	0.011	97.5	0.011	101.7	0.011
5	300	β_x			110.3	0.047	110.9	0.047	110.0	0.048	110.0	0.048	103.1	0.052	104.1	0.050
		β_t			99.4	0.002	101.2	0.002	96.1	0.002	100.9	0.002	87.6	0.002	95.7	0.002
		β_{tx}			102.5	0.004	103.5	0.004	100.4	0.004	103.3	0.004	95.9	0.004	100.8	0.004
5	500	β_x			99.7	0.029	100.3	0.029	99.3	0.030	98.8	0.029	99.4	0.032	100.3	0.031
		β_t			97.7	0.001	99.6	0.001	93.9	0.001	99.0	0.001	87.9	0.001	96.2	0.001
		β_{tx}			99.8	0.002	100.9	0.002	98.0	0.002	100.8	0.002	95.0	0.003	100.0	0.003

Table 11: Simulation results for the MI-GEE based on MNI and OIM methods (K = 5 - Well-balanced distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			105.1	0.289	107.1	0.284	104.4	0.293	108.9	0.281	89.7	0.305	95.2	0.276
		β_t			99.4	0.028	105.4	0.028	87.6	0.030	102.0	0.031	76.1	0.032	97.0	0.034
		β_{tx}			94.4	0.056	96.7	0.056	88.6	0.057	93.7	0.057	81.3	0.059	90.0	0.058
3	300	β_x			118.8	0.083	121.5	0.081	113.6	0.087	120.1	0.085	105.2	0.091	105.0	0.083
		β_t			103.3	0.009	109.5	0.009	90.9	0.010	108.3	0.011	76.0	0.012	94.3	0.012
		β_{tx}			99.8	0.016	102.3	0.016	94.0	0.018	100.7	0.019	86.3	0.020	93.4	0.020
3	500	β_x			103.7	0.049	106.6	0.049	100.4	0.052	106.4	0.050	97.2	0.056	98.2	0.051
		β_t			98.8	0.005	105.1	0.005	87.7	0.006	105.4	0.006	74.3	0.007	92.9	0.007
		β_{tx}			97.7	0.010	100.1	0.010	92.9	0.011	99.6	0.011	87.8	0.012	94.9	0.012
5	100	β_x			87.5	0.155	88.3	0.152	83.4	0.169	83.6	0.164	85.4	0.172	86.3	0.161
		β_t			94.3	0.005	95.6	0.005	89.9	0.006	94.1	0.006	85.8	0.006	94.7	0.007
		β_{tx}			96.7	0.010	97.3	0.010	94.2	0.011	96.3	0.011	92.2	0.012	96.2	0.011
5	300	β_x			88.0	0.044	88.8	0.044	88.8	0.047	89.8	0.046	85.6	0.050	85.6	0.048
		β_t			99.3	0.002	100.7	0.002	95.7	0.002	101.7	0.002	88.1	0.002	99.0	0.002
		β_{tx}			98.0	0.003	98.8	0.003	96.2	0.003	99.3	0.003	92.7	0.004	98.1	0.004
5	500	β_x			88.1	0.026	88.3	0.026	87.2	0.028	87.7	0.027	86.8	0.029	87.6	0.028
		β_t			98.8	0.001	100.2	0.001	94.2	0.001	100.0	0.001	88.4	0.001	100.1	0.001
		β_{tx}			98.2	0.002	98.9	0.002	95.7	0.002	98.8	0.002	93.1	0.002	99.1	0.002

Table 12: Simulation results for the MI-GEE based on MNI and OIM methods (K = 7 - Well-balanced distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			89.7	0.266	91.7	0.258	80.3	0.281	86.3	0.262	79.9	0.300	85.7	0.257
		β_t			81.1	0.029	90.7	0.029	60.7	0.033	77.4	0.033	40.7	0.038	64.6	0.037
		β_{tx}			95.0	0.051	98.3	0.051	87.5	0.053	94.3	0.052	84.0	0.060	89.0	0.057
3	300	β_x			88.4	0.091	91.1	0.090	83.8	0.100	90.4	0.094	76.0	0.112	84.6	0.102
		β_t			78.6	0.011	86.7	0.010	62.0	0.013	81.3	0.012	37.7	0.017	61.9	0.016
		β_{tx}			92.2	0.018	95.0	0.018	86.7	0.019	93.1	0.019	80.9	0.023	89.6	0.022
3	500	β_x			90.0	0.053	93.3	0.052	82.1	0.058	87.9	0.053	74.7	0.066	80.6	0.060
		β_t			81.4	0.005	89.9	0.005	63.7	0.007	83.5	0.006	38.1	0.011	63.0	0.009
		β_{tx}			92.6	0.010	95.7	0.010	85.8	0.011	92.3	0.010	80.3	0.013	87.5	0.013
5	100	β_x			106.6	0.142	107.5	0.141	112.4	0.145	105.6	0.139	106.1	0.158	101.3	0.146
		β_t			99.5	0.005	101.8	0.005	96.0	0.005	100.1	0.005	89.0	0.006	94.6	0.006
		β_{tx}			100.1	0.010	101.3	0.010	99.1	0.011	100.4	0.011	94.6	0.012	97.3	0.012
5	300	β_x			100.8	0.046	100.9	0.046	102.5	0.048	101.1	0.048	104.1	0.052	98.4	0.051
		β_t			99.2	0.002	101.8	0.002	94.3	0.002	100.5	0.002	89.5	0.002	97.6	0.002
		β_{tx}			99.5	0.004	100.8	0.004	97.5	0.004	100.9	0.004	95.3	0.004	100.0	0.004
5	500	β_x			98.0	0.027	98.2	0.027	101.0	0.029	99.3	0.028	101.3	0.031	98.10	0.030
		β_t			99.0	0.001	101.7	0.001	95.6	0.001	102.6	0.001	88.1	0.001	98.5	0.001
		β_{tx}			98.8	0.002	100.2	0.002	96.8	0.002	100.3	0.002	93.7	0.002	99.4	0.002

Table 13: Simulation results for the MI-GEE based on MNI and OIM methods (K = 2 - Skewed distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			104.2	0.680	104.4	0.685	101.0	0.673	101.3	0.687	104.2	0.706	106.1	0.744
		β_t			95.8	0.059	99.8	0.059	74.2	0.066	90.0	0.066	72.8	0.077	98.8	0.081
		β_{tx}			103.9	0.135	104.4	0.137	98.4	0.136	99.0	0.144	103.4	0.151	105.0	0.168
3	300	β_x			103.8	0.214	104.3	0.216	102.9	0.210	104.0	0.217	101.3	0.217	103.6	0.233
		β_t			101.0	0.020	107.7	0.020	87.8	0.021	107.9	0.021	71.7	0.023	107.7	0.024
		β_{tx}			105.5	0.044	106.4	0.045	103.6	0.044	105.4	0.047	101.1	0.046	104.7	0.052
3	500	β_x			101.9	0.120	102.3	0.121	100.8	0.118	102.1	0.122	100.7	0.114	102.9	0.123
		β_t			97.8	0.012	104.1	0.012	81.5	0.013	102.2	0.013	72.6	0.014	108.9	0.015
		β_{tx}			102.2	0.026	102.8	0.027	100.0	0.026	102.3	0.028	101.1	0.025	104.6	0.030

Table 14: Simulation results for the MI-GEE based on MNI and OIM methods (K = 3 - Skewed distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			100.4	0.366	100.0	0.368	100.5	0.355	98.00	0.353	103.0	0.340	99.4	0.333
		β_t			125.3	0.037	113.3	0.038	159.4	0.041	124.5	0.040	205.6	0.048	144.4	0.041
		β_{tx}			100.8	0.073	99.4	0.074	101.7	0.069	96.70	0.072	107.9	0.070	101.1	0.075
3	300	β_x			100.7	0.117	99.9	0.116	101.9	0.115	99.7	0.114	102.1	0.115	98.8	0.114
		β_t			123.5	0.013	109.6	0.013	155.5	0.016	116.9	0.014	199.8	0.023	129.3	0.015
		β_{tx}			101.8	0.024	99.8	0.024	104.5	0.024	99.0	0.025	105.8	0.024	97.7	0.026
3	500	β_x			101.7	0.072	100.8	0.071	102.2	0.069	100.3	0.068	104.2	0.70	101.3	0.070
		β_t			122.8	0.008	108.7	0.008	155.4	0.010	116.5	0.008	201.8	0.018	130.8	0.009
		β_{tx}			103.6	0.014	101.4	0.014	105.3	0.013	100.5	0.014	109.2	0.013	102.0	0.015

Table 15: Simulation results for the MI-GEE based on MNI and OIM methods (K = 4 - Skewed distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			109.3	0.298	107.3	0.289	111.7	0.325	106.4	0.303	117.8	0.338	108.7	0.303
		β_t			108.3	0.032	116.9	0.032	99.8	0.033	114.9	0.035	107.7	0.033	117.0	0.036
		β_{tx}			109.4	0.060	107.3	0.060	111.8	0.065	106.7	0.068	121.1	0.068	111.1	0.070
3	300	β_x			102.9	0.103	101.2	0.100	108.0	0.106	102.9	0.098	110.9	0.120	102.2	0.106
		β_t			91.6	0.011	100.6	0.011	90.4	0.010	107.2	0.011	96.9	0.011	113.0	0.011
		β_{tx}			101.4	0.020	100.1	0.020	108.5	0.019	103.6	0.019	113.0	0.022	103.1	0.023
3	500	β_x			102.5	0.060	100.9	0.058	105.6	0.063	100.7	0.058	110.0	0.072	101.5	0.061
		β_t			91.9	0.006	101.8	0.006	86.2	0.006	103.7	0.006	96.2	0.006	112.3	0.007
		β_{tx}			102.2	0.010	101.1	0.010	105.2	0.011	100.6	0.011	112.4	0.012	103.1	0.013

Table 16: Simulation results for the MI-GEE based on MNI and OIM methods (K = 5 - Skewed distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			101.7	0.321	100.2	0.314	104.4	0.341	99.5	0.331	110.4	0.388	101.0	0.359
		β_t			84.2	0.029	92.1	0.029	73.4	0.034	87.0	0.035	61.4	0.038	70.7	0.040
		β_{tx}			101.3	0.060	99.9	0.060	105.6	0.067	100.0	0.069	115.0	0.080	103.2	0.082
3	300	β_x			99.9	0.097	98.4	0.095	101.9	0.106	97.5	0.101	106.6	0.122	97.9	0.113
		β_t			86.8	0.009	94.4	0.008	73.8	0.010	87.9	0.010	63.2	0.012	76.3	0.013
		β_{tx}			100.9	0.019	99.4	0.019	102.5	0.021	98.0	0.021	110.2	0.025	99.1	0.026
3	500	β_x			100.3	0.056	98.9	0.054	103.7	0.062	99.4	0.058	107.0	0.071	98.7	0.063
		β_t			86.4	0.005	94.9	0.005	77.1	0.006	91.4	0.006	62.5	0.008	76.7	0.008
		β_{tx}			100.3	0.011	99.1	0.011	104.7	0.012	100.2	0.012	109.5	0.014	99.3	0.014

Table 17: Simulation results for the MI-GEE based on MNI and OIM methods (K = 7 - Skewed distribution)

			0%		10%				30%				50%			
					MNI		FCS OIM		MNI		FCS OIM		MNI		FCS OIM	
T	N	Parm	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE	RB(%)	MSE
3	100	β_x			102.5	0.285	101.5	0.277	105.8	0.307	100.6	0.281	109.8	0.337	99.5	0.289
		β_t			81.6	0.028	91.2	0.028	69.2	0.030	88.9	0.029	52.6	0.032	76.7	0.032
		β_{tx}			97.4	0.056	96.8	0.056	102.8	0.060	96.4	0.060	109.3	0.066	95.1	0.064
3	300	β_x			102.7	0.093	101.4	0.091	105.8	0.102	101.7	0.094	108.4	0.114	100.5	0.099
		β_t			92.1	0.008	100.9	0.008	78.2	0.009	102.5	0.009	57.4	0.011	88.0	0.010
		β_{tx}			102.8	0.016	101.8	0.016	106.6	0.018	102.2	0.018	110.4	0.021	99.6	0.020
3	500	β_x			102.8	0.058	101.6	0.057	106.5	0.064	102.4	0.058	109.6	0.074	102.1	0.063
		β_t			88.9	0.005	97.8	0.005	76.3	0.006	99.9	0.005	56.5	0.008	88.7	0.006
		β_{tx}			102.6	0.011	101.4	0.011	107.4	0.012	102.8	0.011	112.9	0.014	102.6	0.013