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Weighted estimating equations for longitudinal studies with death and non-monotone missing time-dependent covariates and outcomes

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SUMMARY

We propose a marginal modeling approach to estimate the association between a time-dependent covariate and an outcome in longitudinal studies where some study participants die during follow up, and both variables have non-monotone response patterns. The proposed method is an extension of weighted estimating equations that allows the outcome and covariate to have different missing-data patterns. We present methods for both random and non-random missing-data mechanisms. A study of functional recovery in a cohort of elderly female hip-fracture patients motivates the approach.

Keywords

Weighted Estimating Equations; Non-monotone Missing Data; Death; Longitudinal Data

1. INTRODUCTION

Non-monotone, or intermittent, missing data can arise for several reasons in studies of the elderly. First, study participants may miss visits, resulting in simultaneously unobserved outcome and covariate data. Also, while attending a study visit, the participant may choose to not respond to particular interview questions or may refuse to perform tests of physical function. In the latter case, the outcome may be observed while the covariate is missing, or vice versa. In addition, high rates of death are often observed in studies of elderly populations. This data structure is a hallmark of gerontologic studies in which participants are followed over time after experiencing an acute injury. In the Baltimore Hip Studies 3 (BHS-3), a cohort of 205 Caucasian women aged 65 years and older who experienced a hip fracture was followed for one year to study factors related to multiple dimensions of recovery. At each follow-up visit (2, 6, and 12 months post hip fracture repair), the women provided serum to assay several biomarkers and performed a battery of physical function tests. One particular analysis focused on describing the association of Interleukin-6 (IL-6), an inflammatory cytokine, with Lower Extremity Gain Scale (LEGS), a summary measure of lower extremity physical function derived from the physical test results, over time [1]. In these data, LEGS and IL-6 are intermittently missing, often with different missing-data patterns within individual. Also, 27 women (13.2%) died during follow-up. Among survivors, 38 out of the $(2^3)^2 = 64$ possible

missing-data patterns are represented in the data. Also, 7 missing-data patterns are represented among those dead by 12 months. Details of the study can be found elsewhere [2,3].

The goal of this paper is to extend weighted estimating equations (WEE) [4,5], a marginal modeling approach for analyzing incomplete data, to account for death and allow both the predictor and outcome to be intermittently missing with different missing-data patterns. In the BHS-3 data, the relationship between IL-6 and LEGS score, both continuous variables, is not defined among the deceased, therefore our goal is to estimate the marginal relationship between these variables among survivors, adjusted for age at the time of hip fracture, and months since hip fracture repair.

Differences in BHS-3 participants' IL-6 and LEGS trajectories across missing-data patterns are not identifiable from observed data. However the underlying process resulting in missing data can fall into one of three broad classes of missing-data mechanisms: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). When data are MCAR, missingness is independent of observed and unobserved variables. Under MAR, the probability of missing is independent of incompletely observed variables, given completely observed variables. Lastly, when data are MNAR, the missing-data mechanism can depend on incompletely observed, given completely observed variables. When data are MCAR or MAR, and the missing-data mechanism parameters are distinct from the data-generating parameters, the data are *ignorably missing*, otherwise, the data are *non-ignorably missing*. [6].

There have been several recent advancements for analyzing longitudinal data subject to non-monotone MNAR missingness. For binary outcomes, Parzen, *et al.* [7] extended earlier work [8] to develop a pseudo-likelihood method for missing outcomes and missing categorical time-dependent covariates, while Minini and Chavance [9] proposed a multiple imputation approach with sensitivity analysis. For continuous outcomes, Lin *et al.* [10] proposed a latent pattern-mixture model approach, while Shen and Weissfeld [11] proposed a copula model, and Yun and Lee [12] developed a hierarchical modeling method.

Recent work for monotone missing data patterns has explicitly differentiated between data unobserved due to drop-out and structurally missing due to death. Kurland and Heagerty [13] and Dufouil *et al.* [14] proposed marginal models for survivors with time-independent covariates. Kurland and Heagerty [13] formally contrasted models that condition on being alive to those where analysis is conditioned on time of death, as in the likelihood-based methods of Pauler *et al.* [15] and Ribaudo *et al.* [16]. All of the above methods were developed for ignorable drop-out, however, only Dufouil *et al.* [14] considered non-ignorable drop-out.

Only one proposed method permits both non-ignorable non-monotone missingness and death. Shen and Gao [17] developed a mixed-effects model for structurally missing outcomes in a two-phased design. However, none of the aforementioned methods allows the missingness patterns of the covariate and outcome to differ, and only one method formally considered the missing-data mechanism of the covariate when the outcome data are incomplete [7].

In order to estimate the relationship between IL-6 levels and LEGS during the year post hip fracture using the BHS-3 data, we aim to extend weighted estimating equations to accommodate the BHS-3 data structure. The paper is organized as follows. In section 2, we formally describe our model and estimation procedure for ignorable missing data. In section 3, we extend the model for non-ignorably missing data. In section 4, we perform a simulation study of our method under various missing-data mechanisms and compare the results to those from other methods. We also investigate the properties of the proposed method with respect to misspecification of the missing-data model. In section 5, we illustrate the method by analyzing the

BHS-3 data. Lastly, in section 6, we discuss the strengths and weaknesses of the method and present ideas for future research.

2. METHODS

(1)

In this section, we define our regression model and estimation procedure for a study consisting of n independent participants and J scheduled visits per person. Let Y_{ij} denote a continuous outcome at the j th visit for person i (e.g., LEGS), where $i = 1, \dots, n$ and $j = 1, \dots, J$. Study participants are assumed to be independent. Let t_j be the visit time of the j th scheduled visit (equal for all participants), X_i be the value of person i 's baseline covariate (e.g., age, observed for all participants), and V_{ij} be the value of a continuous time-dependent covariate for person i at the j th visit (e.g., IL-6 concentration). Let $A_{ij} = 1$ when person i is alive at the time of the j th visit, and $A_{ij} = 0$ otherwise. Then, conditional on being alive ($A_{ij} = 1$), our goal is to estimate the parameters from the following regression equation:

$$\mu_{ij}^{Y|A} = E(Y_{ij} | V_{ij}, X_i, t_j, A_{ij}=1) = \beta_0 + \beta_1 V_{ij} + \beta_2 X_i + \beta_3 t_j. \quad (2)$$

Let S_i denote the time of death for person i , where $S_i > t_j$ implies $A_{ij} = 1$. To avoid modeling $f(S_i)$ and $f(Y_{ij} | S_i)$, the densities of S_i and Y_{ij} given S_i , respectively, we consider semiparametric models of Equation 2 with an independence working correlation for within-person observations.

As described in Kurland and Heagerty [13], specifying a non-independence correlation structure would require conditioning Equation 2 on $S_i = s$, $s > t_j$, resulting in a mean model with a different interpretation than the target of interest. Therefore, parameter estimates are derived from solving independence estimating equations (IEE), a special case of generalized estimating equations (GEE) [18]. When some data are missing, these semiparametric IEE are only unbiased if the data are MCAR, a strong, and likely false, assumption. In order to produce unbiased estimates when data are not MCAR, we appeal to WEE. WEE involve reweighting each observation by the inverse probability of being observed at each time. Efficient WEE were originally developed for missing covariate data in cross-sectional studies [4], and missing outcomes in longitudinal studies [5]. We adapt these approaches to allow both the outcome and time-dependent covariate to be incompletely observed with potentially different missing-data patterns, taking advantage of the independence structure needed for the target of estimation [13]. We emphasize the importance of the independence structure by referring to our method as weighted independence estimating equations (W-IEE). If the data were completely observed for survivors, the estimating equations would be

$$U(\beta) = \sum_{i=1}^n \sum_{j=1}^J A_{ij} \frac{\partial \mu_{ij}^{Y|A}}{\partial \beta} (Y_{ij} - \mu_{ij}^{Y|A}), \quad (3)$$

where β is the vector of regression parameters. When some data are missing, we define $R_{ij}^V = 1$ if V_{ij} is observed at the j th visit for person i and $R_{ij}^V = 0$ if it is missing. Similarly, let $R_{ij}^Y = 1$ (0) if Y_{ij} is observed (missing) at the j th visit for person i . To appropriately weight Equation 3, we need to consider the joint distribution of R_{ij}^V and R_{ij}^Y among survivors at time

$j, P(R_{ij}^V=r_{ij}^V, R_{ij}^Y=r_{ij}^Y|M_{ij}, A_{ij}=1)$, where M is the missing-data model design matrix with vector M_{ij} for person i at visit j . Let $\pi_{ij}^V=P(R_{ij}^V=1|M_{ij}^V, A_{ij}=1)$ and $\pi_{ij}^{Y|R^V}=P(R_{ij}^Y=1|R_{ij}^V, M_{ij}^Y, A_{ij}=1)$, where M_{ij}^V and M_{ij}^Y are person i 's missing-data model design vectors at visit j for R^V and R^Y given R^V , respectively, such that $M_{ij}=M_{ij}^V \cup M_{ij}^Y$.

Under the working independence correlation model, a natural estimating equation would be

$$U(\beta) = \sum_{i=1}^n \sum_{j=1}^J A_{ij} \frac{R_{ij}^Y R_{ij}^V}{\pi_{ij}^{Y|R^V} \pi_{ij}^V} U_{ij}(\beta), \quad (4)$$

where $U_{ij}(\beta) = \frac{\partial \mu_{ij}^{Y|A}}{\partial \beta} (Y_{ij} - \mu_{ij}^{Y|A})$. Equation 4 is unbiased and estimates of β are consistent if Y_{ij} and $R_{ij} = (R_{ij}^V, R_{ij}^Y)$ are correctly modeled. Consistency of the β estimates can be verified by using the iterated expectation to evaluate $E_{[Y, R^Y, R^V|A]}[U(\beta)]$. However, Equation 4 only uses observations where Y and V are both not missing. It has been shown that information about β can be obtained from data points where only V is missing, producing more efficient estimating equations than those from simple inverse probability weighting [4, 19]. To utilize this information, V_{ij} must be modeled. Consider the mean of V_{ij} conditioned on being alive, X_i , and t_j ,

$$\mu_{ij}^{V|A} = E[V_{ij}|X_i, t_j, A_{ij}=1] = \alpha_0 + \alpha_1 X_i + \alpha_2 t_j. \quad (5)$$

When V_{ij} is missing and Y_{ij} is observed, $\mu_{ij}^{(Y|A, -V)} = E[Y_{ij}|X_i, t_j, A_{ij}=1]$ can be specified as a function of β and α by replacing V_{ij} in Equation 2 with $\mu_{ij}^{V|A}$. Information about $\alpha = \{\alpha_0, \alpha_1, \alpha_2\}$ can be obtained by Equation 5 for data points with V_{ij} observed, regardless of the response status of Y_{ij} . Putting these missing-data patterns together, an estimating equation more efficient than Equation 4 can be obtained:

$$U(\gamma) = \sum_{i=1}^n \sum_{j=1}^J A_{ij} \left[\frac{R_{ij}^Y R_{ij}^V}{\pi_{ij}^{Y|R^V} \pi_{ij}^V} U_{ij}^1(\gamma) + \frac{R_{ij}^Y}{\pi_{ij}^{Y|R^V}} \left(1 - \frac{R_{ij}^V}{\pi_{ij}^V} \right) U_{ij}^2(\gamma) + \frac{R_{ij}^V}{\pi_{ij}^V} U_{ij}^3(\gamma) \right], \quad (6)$$

where $\gamma = (\alpha, \beta)$, $U_{ij}^1(\gamma) = \sigma_Y^{-2} \frac{\partial \mu_{ij}^{Y|A}}{\partial \gamma} (Y_{ij} - \mu_{ij}^{Y|A})$, $U_{ij}^2(\gamma) = \sigma_{Y-V}^{-2} \frac{\partial \mu_{ij}^{(Y|A, -V)}}{\partial \gamma} (Y_{ij} - \mu_{ij}^{(Y|A, -V)})$, $U_{ij}^3(\gamma) = \sigma_V^{-2} \frac{\partial \mu_{ij}^{V|A}}{\partial \gamma} (V_{ij} - \mu_{ij}^{V|A})$, $\sigma_Y^2 = \text{Var}[Y_{ij}|V_{ij}, X_i, t_j, A_{ij}=1]$, $\sigma_{Y-V}^2 = \text{Var}[Y_{ij}|X_i, t_j, A_{ij}=1]$, and $\sigma_V^2 = \text{Var}[V_{ij}|X_i, t_j, A_{ij}=1]$. To estimate γ , the quantities π_{ij}^V and $\pi_{ij}^{Y|R^V}$ must be estimated. This task can be accomplished by logistic regression when the missing-data mechanism is random, that is, MCAR or MAR. Logistic regression can be used under two additional missing data mechanisms defined in Kurland and Heagerty [13], MCAR-S and MAR-S.

In general, MCAR and MAR involve modeling the missing data pattern of $R_i = \{R_{i1}, \dots, R_{ij}\}$ conditioned on $A_{ij} = 1$, whereas MCAR-S and MAR-S involve modeling R_i conditioned on $S_i = s$, $s > t_j$. To further contrast MCAR-S and MAR-S with MCAR and MAR, respectively,

consider missing-data mechanisms that only depend on fully-observed variables (i.e., M_{ij} excludes Y , V , and all other incompletely observed auxiliary variables). Let H_{ij}^Y include all variables in M_{ij}^Y except S_i , and define H_{ij}^V analogously. The MAR-S mechanism for Y is $P(R_{ij}^Y | R_{ij}^V, H_{ij}^V, S_i, A_{ij}=1)$, whereas the MAR mechanism reduces this probability to $P(R_{ij}^Y | R_{ij}^V, H_{ij}^Y, A_{ij}=1)$. That is, the MAR-S mechanism for Y at visit j depends on the time of death, S_i (for those alive at visit j), whereas the MAR mechanism only depends on being alive, conditioned on R_{ij}^V and H_{ij}^Y . Similarly, the MCAR-S mechanism for Y is $P(R_{ij}^Y | R_{ij}^V, S_i, A_{ij}=1)$, whereas the MCAR mechanism reduces this probability to $P(R_{ij}^Y | R_{ij}^V, A_{ij}=1)$. The MCAR-S mechanism for Y at visit j depends on the time of death, S_i (for those alive at visit j), whereas the MCAR mechanism only depends on being alive, conditioned on R_{ij}^V . Analogous differences between these four mechanisms for V are seen by comparing $P(R_{ij}^V | H_{ij}^V, S_i, A_{ij}=1)$ (MAR-S) to $P(R_{ij}^V | H_{ij}^V, A_{ij}=1)$ (MAR), and comparing $P(R_{ij}^V | S_i, A_{ij}=1)$ (MCAR-S) to $P(R_{ij}^V | A_{ij}=1)$ (MCAR).

The logistic regressions to perform depend on the factoring of the joint probabilities, based on the missing-data mechanism. Let $\bar{R}_{ij}^V = \{R_{i1}^V, \dots, R_{i(j-1)}^V\}$ and $\bar{R}_{ij}^Y = \{R_{i1}^Y, \dots, R_{i(j-1)}^Y\}$ be the history of R^V and R^Y prior to time j , and are defined to be degenerate when $j = 1$, for person i . Also, let $W_i = \{Y_i, V_i, X_i, t\}$, the collection of complete data for person i , where $t = \{t_1, \dots, t_j\}$, $V_i = \{V_{i1}, \dots, V_{ij}\}$, and Y_i is analogously defined.

At each time j we assume that

$$\begin{aligned} P(R_{ij}=r_{ij} | W_i, R_{i,-j}, S_i=s) &= P(R_{ij}^Y=r_{ij}^Y | R_{ij}^V=r_{ij}^V, R_{i,-j}, W_i, S_i=s) \\ &\times P(R_{ij}^V=r_{ij}^V | R_{i,-j}, W_i, S_i=s) \\ &= P(R_{ij}^Y=r_{ij}^Y | R_{ij}^V=r_{ij}^V, \bar{R}_{ij}, W_i, S_i=s) \\ &\times P(R_{ij}^V=r_{ij}^V | \bar{R}_{ij}, W_i, S_i=s), \end{aligned} \quad (7)$$

where $R_{i,-j} = \{R_{i1}, \dots, R_{i(j-1)}, R_{i(j+1)}, \dots, R_{ij}\}$.

Equation 7 means that the response pattern at visit j is conditionally independent of responses after visit j . Further simplification of Equation 7 depends on additional assumptions about the missing-data mechanism. We begin by imposing several reasonable assumptions. First, we assume that R_{ij}^Y and R_{ij}^V do not depend on the values of Y and V after visit j , conditioned on data up to visit j . Second, R_{ij}^Y and R_{ij}^V only depend on time at visit j (t_j), conditioned on data up to visit j . Let V_{ij}^- and Y_{ij}^- be the histories of V and Y , respectively, prior to time j , and $W_{ij} = \{Y_{ij}^-, V_{ij}^-, X_i, t_{j-1}\}$ for person i . These assumptions imply

$$\begin{aligned} &P(R_{ij}^Y=r_{ij}^Y | R_{ij}^V=r_{ij}^V, \bar{R}_{ij}, W_i, S_i=s) \\ &= P(R_{ij}^Y=r_{ij}^Y | R_{ij}^V=r_{ij}^V, \bar{R}_{ij}, W_{i(j+1)}, S_i=s), \end{aligned} \quad (8)$$

and

$$\begin{aligned}
 & P\left(R_{ij}^V=r_{ij}^V|\bar{R}_{ij}, W_i, S_i=s\right) \\
 & =P\left(R_{ij}^V=r_{ij}^V|\bar{R}_{ij}, W_{i(j+1)}, S_i=s\right).
 \end{aligned}
 \tag{9}$$

Specification of the model is only relevant for survivors, as $P\left(R_{ij}^V=R_{ij}^Y=0|S_i \leq t_j\right) \equiv 1$. When both Y and V are MCAR, Equation 8 equals $P\left(R_{ij}^Y=r_{ij}^Y|R_{ij}^V=r_{ij}^V, S_i>t_j\right)$, and Equation 9 equals $P\left(R_{ij}^V=r_{ij}^V|S_i>t_j\right)$. When Y and V are MCAR-S, missingness also depends on the actual time of death, not just on being alive. Therefore, Equation 8 equals $P\left(R_{ij}^Y=r_{ij}^Y|R_{ij}^V=r_{ij}^V, t_j, S_i=s, S_i>t_j\right)$, and Equation 9 equals $P\left(R_{ij}^V=r_{ij}^V|t_j, S_i=s, S_i>t_j\right)$. MAR and MAR-S missing-data mechanisms are functions of observed covariate and outcome history data. Let $W_{ij}^* = \left\{ \bar{R}_{ij}^Y Y_{ij}, \bar{R}_{ij}^V V_{ij}, X_i, t_j \right\}$, where $\bar{R}_{ij}^Y Y_{ij} = \left\{ R_{i1}^Y Y_{i1}, \dots, R_{i(j-1)}^Y Y_{i(j-1)} \right\}$, and $\bar{R}_{ij}^V V_{ij}$ is analogously defined. When Y and V are MAR, Equation 8 equals $P\left(R_{ij}^Y=r_{ij}^Y|R_{ij}^V=r_{ij}^V, \bar{R}_{ij}, W_{ij}^*, R_{ij}^V V_{ij}, S_i>t_j\right)$, and Equation 9 equals $P\left(R_{ij}^V=r_{ij}^V|\bar{R}_{ij}, W_{ij}^*, S_i>t_j\right)$. Lastly, when Y and V are MAR-S, Equation 8 is $P\left(R_{ij}^Y=r_{ij}^Y|R_{ij}^V=r_{ij}^V, \bar{R}_{ij}, W_{ij}^*, S_i=s, S_i>t_j\right)$, and Equation 9 is $P\left(R_{ij}^V=r_{ij}^V|\bar{R}_{ij}, W_{ij}^*, S_i=s, S_i>t_j\right)$. When the missingness is MCAR, weights need not be estimated, as those who are observed are a random sample of survivors. However, for the other three missing data mechanisms, weights are estimated by logistic regression at each time among survivors. A more complex method is required when data are MNAR, a mechanism considered in the next section. Thus far, it has been assumed that V is a continuous predictor. This approach can also be used for a categorical or binary V , as it has been shown in Parzen *et al.* [19] that wrongly using a normal working model for a missing covariate in WEE for linear regression has little impact on the consistency of parameter estimates.

3. MNAR MECHANISM

When data are assumed to be MNAR, that is, missingness depends on quantities that are themselves incompletely observed, an alternative procedure is required to estimate the weights. Data that are MNAR are challenging because the relationship between the response indicator and the incompletely observed variable is not identifiable. In this case, the best that can be accomplished is a sensitivity analysis based on various assumptions of this relationship [20]. The estimation strategy extends that used by Dufouil *et al.* [14] for drop-outs in a mortal cohort. We estimate weights for both the outcome and time-dependent covariate. Consider the following case of MNAR:

$$\begin{aligned}
 & P\left(R_{ij}^Y=r_{ij}^Y|R_{ij}^V=r_{ij}^V, \bar{R}_{ij}, W_i, S_i=s\right) = \\
 & P\left(R_{ij}^Y=r_{ij}^Y|R_{ij}^V=r_{ij}^V, R_{i(j-1)}^Y, t_j, Y_{ij}, S_i=s, S_i>t_j\right),
 \end{aligned}$$

and

$$P\left(R_{ij}^V=r_{ij}^V|R_{ij}^V, W_i, S_i=s\right)=P\left(R_{ij}^V=r_{ij}^V|R_{i(j-1)}^V, t_j, V_{ij}, S_i=s, S_i>t_j\right).$$

The probability of missing $Y(V)$ at time j depends on the values of $Y(V)$ at time j and the time of death. For an assumed logistic model, the coefficient for, say t_j , in each model can be estimated by equations motivated by the score equations for generalized linear models [21]:

$$\sum_{i=1}^n A_{ij} \frac{1}{\pi_{ij}^{Y|R^V}} \left(R_{ij}^V - \pi_{ij}^{Y|R^V} \right) t_j = 0 \quad (10)$$

$$\sum_{i=1}^n A_{ij} \frac{1}{\pi_{ij}^V} \left(R_{ij}^V - \pi_{ij}^V \right) t_j = 0. \quad (11)$$

When $Y_{ij}(V_{ij})$ is missing, Equation 10 (11) simplifies to $-A_{ij}t_j$. V can be added to the missing-data model for Y using weighted estimating equations, where Equation 10 is multiplied by

$\frac{R_{ij}^V}{\pi_{ij}^V}$ when V_{ij} is observed. When V_{ij} is missing, it is integrated out of Equation 10, and the

resulting equation is multiplied by $1 - \frac{R_{ij}^V}{\pi_{ij}^V}$. When V is categorical, the integration is straightforward. For continuous V , like that in the BHS-3 data, the integration requires numerical methods.

4. SIMULATION STUDY

To evaluate the properties of the proposed method, we performed simulation studies with $J = 4$ repeated measures. Each study was based on $N_{sim} = 1000$ iterations of samples consisting of $N = 200$ individuals.

Three different missing-data mechanisms were examined in this study: MAR, MAR-S, and MNAR. The specific missing-data models are shown in Table I. The simulation proceeded as follows. First, $X \sim \text{Normal}(1, 4)$, a baseline covariate, was simulated. In this study, survival time is the first visit that cannot be attended due to death. Therefore, survival time S was simulated from a multinomial distribution with $S \in \{2, 3, 4, 5\}$, where all are alive at the first visit, and $S = 5$ denotes survival past the end of study, and the cumulative incidence of death is 16%, 26%, and 33% at visits two, three, and four, respectively. Conditional on X and S , a normally-distributed, time-dependent variable, with variance 1, V , was simulated with mean

$$E[V_{ij}|X_i, t_j, S_i] = 0.20 + 0.10X_i + 0.10(t_j - 1).$$

An exchangeable covariance structure with correlation 0.5 was assumed for V . Conditional on X , V , and S , the outcome Y was simulated from a normal distribution with mean

$$E[Y_{ij}|V_{ij}, X_i, t_j, S_i] = (0.40S_i + 0.50) + (0.40S_i - 1)V_{ij} + (0.40S_i + 0.20)X_i + (0.40S_i + 0.50)(t_j - 1),$$

variance 1, and exchangeable covariance structure with correlation 0.7. This simulation model is not conditioned on being alive, and hence, is not the target of interest. The true parameters of the target of interest, found by solving Equation 3, are

$$\mu_{ij}^{(Y|A)} = 1.58 + 2.37I_{(t_j=2)} + 4.75I_{(t_j=3)} + 7.03I_{(t_j=4)} + 0.46V_{ij} + 1.66X_i.$$

Conditioned on being alive, R^V was simulated at each time from a Bernoulli distribution according to the assumed missing-data model in Table I. Conditioned on R^V , R^Y for survivors was also simulated at each time from a Bernoulli distribution. Logistic models for both R^V and R^Y were assumed. These specifications resulted in, on average, 40–60% data points missing at least one of (10%–15% missing both) Y and V at each visit among survivors.

Two types of simulation studies were performed. First, for all three missingness mechanisms, the proposed method using Equation 6 was compared to two popular alternative approaches, unweighted IEE (linear regression) and weighted GEE (W-GEE) using an exchangeable correlation matrix. For each simulated data set, bootstrap standard errors were estimated for W-IEE and W-GEE by taking $N_{bs} = 200$ bootstrap samples of the data. Bootstrap standard errors are numerically intensive to calculate, therefore robust standard errors based on the Huber-White information sandwich [22, 23] were explored as an alternative. IEE and W-GEE are expected to yield inconsistent estimates for for MAR, MAR-S, and MNAR missing data. Estimates for IEE are expected to be inefficient because the method uses less data than W-IEE. Standard errors from W-GEE may be smaller or larger compared to those from W-IEE, because, although the method uses less data, the non-independence weights implicitly impute missing outcomes and account for intra-subject correlation. In the second part of the simulation study, the impact of misspecifying the missing-data model on W-IEE results is explored. Data are modeled as MAR for true MNAR and MAR-S missingness, and modeled as MAR-S for true MNAR missingness. Also, when data are MAR, we explore two misspecified models: R^Y correctly modeled as MAR, R^V incorrectly modeled as MCAR (called MAR-Y) and R^V correctly modeled as MAR, R^Y incorrectly modeled as MCAR (called MAR-V).

Comparisons between IEE, W-IEE, and W-GEE when the missing-data process is correctly specified are found in Table II. W-IEE has the best coverage and produces estimates closest to the truth for all three missing-data mechanisms. W-GEE produces the worst coverage and the most biased estimates, with the exception of the coefficient of V . IEE produces the largest standard errors, except for the coefficient of V . The standard errors for W-IEE are comparable to those from W-GEE, with the exception of the coefficient for V , which has a smaller standard error when estimated by W-GEE. Comparing the bootstrap standard error to the empirical standard error shows that W-IEE with the bootstrap produces accurate standard error estimates.

We explored the dependence of W-GEE results on the choice of correlation matrix by fitting W-GEE using the unstructured correlation matrix instead of the exchangeable matrix. We found that using the unstructured correlation matrix had little impact on bias compared to using the exchangeable matrix (when the data were generated using an exchangeable matrix), however the simulation standard errors differed wildly from the empirical standard errors (data not shown). The instability of standard errors using the unstructured correlation matrix is not surprising considering the small sample size, high proportion of missing data specified in the simulations, and large number of additional parameters that need to be estimated in the unstructured correlation matrix relative to the exchangeable correlation matrix.

Results of the model mis-specification simulation study are found in Table III. For most combinations of true and assumed missing-data mechanisms, coverage probabilities dropped below the nominal 95%. The largest bias was produced for the intercept and V . Little bias and no drop in coverage occurred when both V and Y were MAR, but V was incorrectly assumed to be MCAR. This result is due to the missingness of V only depending on Y indirectly through quantities accounted for in the model. Specifically, V at the previous visit among those present at the previous visit is related directly to missingness and indirectly to Y at the current visit through its dependence on the value of V at the current visit [24]. Interestingly, model mis-specification using W-IEE has a less deleterious impact on estimation properties than using W-GEE or IEE with the correct model. The degree of bias in parameter estimates is greater and coverage is lower when W-GEE and IEE are used with the correct missing-data model than when W-IEE is used with the incorrect missing-data model.

The simulation results for misspecified models exemplify theoretical properties of $U(\gamma)$ (Equation 6). The mean $\mu_{ij}^{(Y|A)}$ is consistently estimated if $E[U(\gamma)] = 0$. This is true when weights and regression models are specified such that

$$E \left[\frac{R_{ij}^Y R_{ij}^V Y_{ij}}{\pi_{ij}^{Y|R^V} \pi_{ij}^V} | X_i, V_{ij}, t_j, A_{ij}=1 \right] = \mu_{ij}^{(Y|A)}$$

$$E \left[\frac{R_{ij}^Y}{\pi_{ij}^{Y|R^V}} \left(1 - \frac{R_{ij}^V}{\pi_{ij}^V} \right) | X_i, t_j, A_{ij}=1 \right] = 0$$

and

$$E \left[\frac{R_{ij}^V V_{ij}}{\pi_{ij}^V} | X_i, t_j, A_{ij}=1 \right] = \mu_{ij}^{(V|A)}$$

Covariates related to R^Y and Y (or R^V and V), even if not of interest in the regression equation, are needed in the missing-data model to consistently estimate regression parameters [4,5]. This property explains why omitting S from the missing-data models when data are MAR- S produces biased estimates. Bias would also occur if X was related to R^Y or R^V and omitted from the missing-data models.

The proposed method performed well for sample sizes as small as $N = 200$. The bootstrap produced standard errors close to the empirical standard errors resulting in confidence interval coverage near or above the nominal 95% (Table II). We found that robust standard errors for the coefficients of V and X were under-estimated and those for the remaining coefficients were over-estimated using W-IEE. With $N = 200$ and MNAR data, the standard errors for V and X coefficients were, on average, 0.08 and 0.05, resulting in 91.1% and 83.1% coverage, respectively. When data were MAR, estimated robust standard errors for V and X coefficients of 0.10 and 0.06 resulted in 91.9% and 87.2% coverage, respectively. Lastly, when data were MAR- S , the estimated robust standard errors for V and X coefficients were 0.08 and 0.05, producing 91.1% and 83.1% coverage, respectively.

Analysis using Equation 4 was also performed. The estimated coefficients varied little from those using the more efficient W-IEE approach. The standard errors for the coefficient for V

from both methods were within 1.0% of each other across the missing data mechanisms. However, the estimated standard errors for the other parameters using Equation 4 were 8%–31% larger than those estimated using W-IEE (results not shown).

5. BHS-3 DATA APPLICATION

We now return to the BHS-3 data set. Injured elderly cohorts are subject to the competing forces of recovery over time and functional decline due to complications associated with advancing age. Not surprisingly, the two most common missing data patterns in the BHS-3 data were those in which late visits were missed and early visits were observed and those in which late visits were observed and early visits were missed, 32 and 26 participants, respectively. Thirty participants both performed the lower extremity function tests and provided serum at all visits, and 101 provided only one of serum or lower extremity function test results at each visit. Other non-monotone patterns were observed for the remaining 16 participants. The numbers providing serum at each follow-up visit, 2, 6, and 12 months post-fracture, were 95, 101, and 82, respectively. The numbers performing the lower extremity function tests at each follow-up visit were 81, 89, and 77, respectively. The numbers providing both serum and LEGS data at 2, 6, and 12 months were 65, 78, and 59, respectively. The cumulative number of women who missed visits due to death was 7, 15, and 27, respectively.

In this analysis $t_j = j$, where $j = 1, 2, 3$, Y_{ij} is LEGS score and V_{ij} is IL-6 for person i at time j , and X_i is baseline age in years. Lastly, S_i was the first visit that person i could not attend due to death, where $S_i = 4$ denotes being alive at 12 months post fracture repair. In these data, the median age (range) was 82 (65–96) years. The median (interquartile range [IQR]) levels of IL-6 at 2, 6, and 12 months post hip fracture among those who provided serum were, 11.97 (5.67–0.87) pg/ml, 7.62 (4.65–20.79) pg/ml, and 7.38 (3.99–15.85) pg/ml, respectively. LEGS scores ranged from 0 to 36, where higher scores correspond to better lower extremity function. The mean (standard deviation) LEGS scores at 2, 6, and 12 months post-fracture among those who performed the lower extremity tasks were 18.8 (8.1), 23.7 (8.3), and 25.0 (8.0). These estimates suggest that, on average, levels of IL-6 decline and lower extremity function improves over time. However, these estimates may be biased due to differential follow-up, and cannot be interpreted as mean trajectories due to the non-monotone missing data patterns for both IL-6 and LEGS.

The data were analyzed based on four missing data mechanisms: MCAR, MAR, MAR-S, and MNAR. Weights were estimated according to the logistic models used in the simulation study (Table I). For the MNAR mechanism, several values for the coefficients of Y_{ij} and V_{ij} were considered. Those with better lower extremity function were assumed to be more likely to provide a LEGS score than those with worse lower extremity function, and those who had lower IL-6 concentrations were assumed to be more likely to provide serum than those with higher IL-6 concentrations. Denote the coefficient for $Y(V)$ for the logistic model of π^{Y/R^V} (π^V) as $\beta_R^{Y/Y}(\beta_R^{V/V})$. The combinations of $(\beta_R^{Y/Y}, \beta_R^{V/V})$ examined in the MNAR analysis are: $\{(0, 0), (0.05, 0), (0, -0.10), (0.05, -0.10)\}$. Note that the combination (0, 0) corresponds to MCAR-S.

Parameter estimates and 95% confidence intervals are provided in Table IV for MCAR, MAR and MAR-S models and in Table V for MNAR models. Estimated coefficients using W-IEE differed little between the MAR and MAR-S missing-data mechanisms. With the exception of the coefficient for IL-6, estimates using W-GEE more closely resembled those from IEE than those from W-IEE. This result is likely due to the additional data utilized with the W-IEE method. For example, the six-month and twelve-month median (IQR) of IL-6 among those with observed LEGS scores were 6.92 (4.15, 12.63) pg/ml and 6.56 (4.00, 16.29) pg/ml, respectively. The analogous results for those with missing LEGS scores (i.e., data only utilized

by W-IEE) were 21.93 (11.83, 35.25) pg/ml and 9.65 (4.57, 12.87) pg/ml at six and twelve months, respectively.

Figure 1 shows mean response profiles based on seven different missing-data models estimated using IEE and W-IEE for a BHS-3 participant with baseline age at the mean (82 years) and IL-6 levels at the responder medians at 2, 6, and 12 months post hip fracture; 11.97 pg/ml, 7.62 pg/ml, and 7.38 pg/ml, respectively. Assuming data are MNAR with $(\beta_{R^Y/Y}, \beta_{R^V/V}) = (0.05, 0)$ results in the lowest mean LEGS scores compared to the other missing-data models. In contrast, assuming MCAR (using IEE) results in the highest mean LEGS trajectory. Figure 1 shows little difference between trajectories fit assuming MAR and MAR-S, whereas the difference in trajectories between MCAR and MNAR with $(\beta_{R^Y/Y}, \beta_{R^V/V}) = (0, 0)$ is large.

Parameter estimates using W-IEE were sensitive to MNAR assumptions about the missing-data model. The estimated coefficient for IL-6 ranged from -0.02 for combination $(0, -0.10)$ to -0.07 for combination $(0.05, 0)$. These results show that estimates in these data are more sensitive to assumptions about R^Y than R^V . The estimated coefficient for age was also sensitive to the missing-data model. Although age was not directly accounted for when estimating the weights, it indirectly impacted the weight estimates through its association with LEGS (correlation $= -0.38$). Although the estimates differed across missing-data models, the qualitative conclusions did not. In all cases, higher levels of IL-6, a marker for inflammation, are associated with worse lower extremity function at any given time, controlling for age and conditioned on being alive. Also, older age is associated with worse lower extremity function at any given time, controlling for IL-6 and conditioned on being alive. Across assumptions, estimated adjusted mean LEGS scores are higher at twelve months compared to two and six months, adjusted for age and IL-6 and conditioned on being alive. Except for the MNAR combination $(0.05, -0.10)$, estimated adjusted mean LEGS scores at six months are higher than at two months. The differences in estimates at six months compared to two months between W-IEE and IEE reflect the modeling assumption of the weights that those with worse function tend to be missing, implying that the observed sample at six months is biased toward better lower extremity function.

For each missing-data model, the estimated coefficient for IL-6 is smaller for W-GEE than W-IEE. The standard errors for W-GEE tend to be larger than those for W-IEE, due to the large amount of missing data. The estimated time effect is particularly sensitive to assumptions about the missing-data model, due to assumptions about the observed cohort relative to the whole cohort at each time.

6. DISCUSSION

This paper extends weighted estimating equations to general missing data patterns for incomplete outcomes and a time-dependent covariate. W-IEE extracts information from observations with missing covariate data, producing consistent parameter estimates conditioned on being alive that are more efficient than those from either IEE or W-GEE. This method is particularly useful in longitudinal studies of aging populations where the incidence of death is high and missing data often do not follow a monotone pattern. W-IEE utilize death information after drop-out and can handle MNAR data via a sensitivity analysis approach.

Our method follows the example of Kurland and Heagerty [13] by explicitly focusing on estimation conditioned on being alive. The simulation studies and application to the BHS-3 data exemplify the importance of choosing the correct estimation method for this goal, independent of specifying the missing-data mechanism. Based on the simulation results, we recommend using bootstrap standard errors in lieu of robust standard errors.

Simulations demonstrated that W-IEE performs well when the missing-data mechanism is correctly specified. However, results can be biased when the model is misspecified. The missing-data mechanism is generally unknown and cannot be identified by the observed data, therefore it is important to collect additional information to understand the reasons for missingness. Study designs can incorporate approaches such as making follow-up phone calls to reschedule missed appointments and inquiring to the participant or a proxy (e.g., spouse or other care taker) regarding the reason for missed visits or refusal for specific items such as answering interview questions, performing physical function tests, and providing biological specimens. Rescheduling missed appointments can reduce the proportion of missing data, which would decrease the sensitivity of results to model misspecification. Information about missingness can be incorporated into the model by, for example, assuming different coefficients for Y and V in the MNAR model depending on the reason for refusal. Also, the dependence of missingness on auxiliary variables that are not of direct scientific interest can be explored.

The BHS-3 example included one time-dependent covariate and the same visit schedule for each participant. The W-IEE approach can accommodate generalizations for multiple time-dependent covariates and different visit schedules. For this data structure, $j = 1, \dots, J_i$, and t_{ij} is the j th scheduled visit for the i th participant. Let K be the number of time-dependent covariates, then $(1 + K)\max(J_i)$ missing-data models are to be fit, one for each visit-by-time-dependent variable (K covariates and one outcome) combination. Let $V_1, \dots, V_K$ denote the

time-dependent covariates. The missing-data models are $\pi_{ij}^{Y|R^{-\bar{V}}}, \pi_{ij}^{V_K|R^{-\bar{V}_K}}, \pi_{ij}^{V_{K-1}|R^{-\bar{V}_{K-1}}}, \dots, \pi_{ij}^{V_1}$, where $R^{-\bar{V}} = \{R^{V_K}, R^{V_{K-1}}, \dots, R^{V_1}\}$, and $R^{-\bar{V}_k} = \{R^{V_{K-1}}, \dots, R^{V_1}\}$. The second term in Equation (5) is replaced by $2^K - 1$ terms, one for each missing-data pattern where the outcome is observed and at least one covariate is missing. The third term in Equation (5) is replaced by $2^K - 1$ terms to estimate the mean models for each covariate V_k conditioned on the $V_1, \dots, V_{k-1}$ that are observed. Patterns not observed need not be estimated, thus the upper bound on the number of extra terms in Equation 5 is $1 + 2(2^K - 1) = 2^{K+1} - 1$. In the BHS-3 example, if we included in the model additional biomarkers assayed using serum, neither additional missing data models nor additional mean models in Equation (5) would be needed because, ignoring laboratory error, all biomarkers would have the same missing-data pattern. However, if time-dependent self-reported medication use [e.g., non-steroidal anti-inflammatory drugs (NSAIDS)] was included in the model, then $K = 2$, therefore $3 \times 3 = 9$ missing-data models would be estimated, and $2^3 - 1 = 7$ mean models in Equation (5) would be estimated. However, if some missingness patterns between LEGS, IL-6, and NSAIDS were unobserved, fewer models need to be specified.

Including in the model additional time-dependent covariates that are incompletely observed results in an increased number of parameters to be estimated. Thus, when the sample size is small, and more than one time-dependent covariate is modeled, additional assumptions to reduce the number of parameters may be needed to produce stable estimates. Although the methodology can accommodate visit schedules that vary between participants, having visit schedules is crucial. In the absence of visit schedules, the problem is better formulated in the rubric of informative observation times (i.e., the underlying outcome influences observation times) rather than missing data [25].

The most challenging aspects of our method are estimating standard errors from the bootstrap and the limited utility of off-the-shelf statistical packages in efficiently incorporating observations with missing covariates. Although our method provides improvement in efficiency compared to others (e.g., simple inverse probability weighting), it does not fully utilize the vector of response indicators for intermittent missing outcomes when estimating the weights as described by Robins *et al.* [5], where the probability of each possible realization of the vector

is estimated. However, when the number of missing-data patterns is large, as with the BHS-3 data, the proposed model provides a useful lower-dimensioned approach to use all available data to model the missing-data mechanism of both incompletely observed outcomes and time-dependent covariates.

Inverse probability weighting is one of many classes of methods for analysis with missing data. In subsequent research, we will explore alternative methods for analyzing longitudinal data with death and non-monotone missing outcomes and covariates including several multiple imputation procedures, Bayesian analysis, and likelihood-based analysis using pattern-mixture and selection models.

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Figure 1. Mean BHS-3 response profiles by missing-data model estimated using IEE (MCAR) and W-IEE (all others).

Table I

Simulation study models

Missing-Data Model Logistic Simulation Model

MAR	$\text{Logit}\left(\pi_{ij}^V\right) = 0.50 + \left[0.10R_{i(j-1)}^V V_{i(j-1)} - 0.10(1 - R_{i(j-1)}^V)\right]I_{j>1}$
	$\text{Logit}\left(\pi_{ij}^{Y R^V}\right) = 0.50 + 0.10R_{ij}^V V_{ij} - 0.10(1 - R_{ij}^V) + \left[0.10R_{i(j-1)}^Y Y_{i(j-1)} - 0.10(1 - R_{i(j-1)}^Y)\right]I_{j>1}$
MAR-S	$\text{Logit}\left(\pi_{ij}^V\right) = 0.50 + 0.15S_i \left[0.10R_{i(j-1)}^V V_{i(j-1)} - 0.10(1 - R_{i(j-1)}^V)\right]I_{j>1}$
	$\text{Logit}\left(\pi_{ij}^{Y R^V}\right) = 0.50 + 0.15S_i + 0.10R_{ij}^V V_{ij} - 0.10(1 - R_{ij}^V) + \left[0.10R_{i(j-1)}^Y Y_{i(j-1)} - 0.10(1 - R_{i(j-1)}^Y)\right]I_{j>1}$
MNAR	$\text{Logit}\left(\pi_{ij}^V\right) = 0.50 + 0.05S_i - 0.25V_{ij} + 0R_{i(j-1)}^V$
	$\text{Logit}\left(\pi_{ij}^{Y R^V}\right) = 0.50 + 0.05S_i + 0.20Y_{ij} + 0R_{i(j-1)}^Y + 0R_{ij}^V$

Table II

Simulation study results ($N_{sim} = 1000$, $N_{bs} = 200$, $N = 200$); percent bias of β $100(\hat{\beta} - \beta)/\beta$, standard error for $\hat{\beta}$ (SE), empirical standard error for $\hat{\beta}$ (ESE), and 95% confidence interval coverage probability (95% CI coverage)

Effect	β	Method	MAR				MAR-S				MNAR			
			Percent Bias	SE	ESE	95% CI Coverage	Percent Bias	SE	ESE	95% CI Coverage	Percent Bias	SE	ESE	95% CI Coverage
Intercept	1.58	W-IEE IEE	-0.4 0.3	0.15 0.19	0.15 0.19	0.969 0.943	-0.2 5.6	0.13 0.15	0.13 0.15	0.946 0.905	0.5 7.8	0.13 0.16	0.13 0.16	0.959 0.875
Time 2	2.37	W-GEE	7.7	0.18	0.16	0.873	7.8	0.14	0.14	0.831	7.0	0.14	0.15	0.881
		W-IEE IEE	0.3 1.0	0.18 0.23	0.17 0.24	0.965 0.941	0.1 -2.0	0.14 0.18	0.14 0.18	0.944 0.938	-0.2 -3.2	0.14 0.18	0.14 0.19	0.940 0.922
Time 3	4.75	W-GEE	-6.2	0.19	0.19	0.865	-7.6	0.13	0.13	0.704	-7.1	0.14	0.14	0.728
		W-IEE IEE	-0.1 0.1	0.18 0.23	0.17 0.23	0.963 0.945	0.1 -2.1	0.15 0.18	0.16 0.18	0.948 0.900	-0.1 -2.7	0.15 0.18	0.14 0.18	0.954 0.878
Time 4	7.03	W-GEE	-6.1	0.20	0.19	0.649	-7.3	0.14	0.14	0.302	-6.9	0.14	0.15	0.375
		W-IEE IEE	0.0 0.0	0.18 0.23	0.17 0.23	0.967 0.951	0.0 -1.7	0.16 0.18	0.16 0.18	0.954 0.883	-0.2 -2.1	0.15 0.18	0.15 0.18	0.957 0.864
V	0.46	W-GEE	-5.3	0.20	0.19	0.499	-6.3	0.14	0.14	0.156	-6.0	0.14	0.15	0.220
		W-IEE IEE	0.2 3.5	0.11 0.10	0.11 0.10	0.931 0.930	-0.2 7.1	0.09 0.08	0.09 0.09	0.953 0.936	0.7 5.6	0.10 0.09	0.10 0.09	0.935 0.924
X	1.66	W-GEE	1.9	0.09	0.09	0.940	2.0	0.08	0.08	0.933	4.2	0.08	0.08	0.924
		W-IEE IEE	0.1 0.6	0.08 0.08	0.08 0.08	0.942 0.934	0.1 1.6	0.07 0.07	0.07 0.07	0.959 0.918	-0.1 0.8	0.07 0.07	0.07 0.08	0.948 0.934
		W-GEE	-2.6	0.10	0.10	0.936	-4.2	0.09	0.10	0.894	-4.2	0.09	0.09	0.910

Table III

Simulation study results: Impact of model mis-specification for W-IEE ($N_{sim} = 1000, N_{bs} = 200, N = 200$); percent bias of β , 95% confidence interval coverage probability (95% CI coverage)

True model:		MAR			MAR-V			MAR-S			MNAR		
		MAR-Y		MAR		MAR		MAR		MAR		MAR-S	
Effect	β	Percent Bias	95% CI Coverage	Percent Bias	Coverage	Percent Bias	Coverage	Percent Bias	95% CI Coverage	Percent Bias	95% CI Coverage	Percent Bias	95% CI Coverage
Intercept	1.58	0.1	0.960	0.7	0.950	3.1	0.936	6.9	0.863	5.1	0.906		
Time 2	2.37	0.4	0.957	1.3	0.959	-1.8	0.943	-2.8	0.914	-1.4	0.938		
Time 3	4.75	0.3	0.965	0.2	0.961	-1.5	0.917	-1.7	0.904	-0.8	0.933		
Time 4	7.03	0.1	0.972	0.0	0.961	-1.0	0.912	-1.1	0.919	-0.6	0.931		
V	0.46	0.0	0.959	5.2	0.938	5.5	0.920	3.8	0.944	3.2	0.929		
X	1.66	0.2	0.950	0.5	0.948	0.4	0.929	0.0	0.956	-1.6	0.940		

BHS-3 analysis results for MCAR, MAR, and MAR-S models ($N = 205$, $N_{bs} = 200$), estimate ($\hat{\beta}$) and standard error (SE)

Model:	MCAR		MAR		MAR-S	
	IEE		W-IEE		W-IEE	W-GEE
Effect	β (SE)		β (SE)		β (SE)	β (SE)
Intercept	43.07 (9.36)		49.18 (9.03)		44.52 (10.53)	44.90 (9.72)
6 Months	4.84 (1.04)		1.78 (1.62)		3.31 (1.12)	3.62 (1.15)
12 Months	6.09 (1.18)		6.06 (2.33)		5.72 (1.15)	5.84 (1.10)
IL-6	-0.04 (0.03)		-0.07 (0.04)		-0.06 (0.04)	-0.06 (0.04)
Age	-0.29 (0.12)		-0.37 (0.11)		-0.36 (0.10)	-0.32 (0.12)

BHS-3 analysis results for MNAR models ($N = 205$, $N_{b_{\text{rs}}} = 200$), estimate (β) and standard error (SE)

$\beta_{R^Y \text{rs}} \beta_{R^Y \text{V}}:$		0, 0	0.05, 0	0, -0.10	0.05, -0.10
Effect	Method	β (SE)	β (SE)	β (SE)	β (SE)
Intercept	W-IEE	46.38 (8.96)	44.02 (9.88)	49.77 (11.04)	54.31 (13.38)
	W-GEE	44.96 (15.27)	46.13 (18.08)	43.81 (23.29)	46.55 (41.38)
6 Months	W-IEE	2.44 (1.78)	1.47 (1.91)	2.18 (2.05)	-0.37 (2.51)
	W-GEE	4.62 (1.48)	1.87 (2.10)	5.50 (3.33)	1.09 (4.78)
12 Months	W-IEE	6.09 (2.08)	4.65 (2.72)	5.65 (2.17)	3.04 (2.91)
	W-GEE	5.87 (1.24)	5.19 (2.68)	5.26 (3.43)	4.10 (5.52)
IL-6	W-IEE	-0.03 (0.03)	-0.07 (0.04)	-0.02 (0.05)	-0.06 (0.06)
	W-GEE	-0.02 (0.03)	-0.03 (0.10)	-0.01 (0.05)	-0.03 (0.11)
Age	W-IEE	-0.34 (0.11)	-0.32 (0.12)	-0.38 (0.13)	-0.42 (0.15)
	W-GEE	-0.33 (0.20)	-0.38 (0.23)	-0.32 (0.29)	-0.38 (0.50)