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Bayesian Latent-class Mixed-effect Hybrid Models for Dyadic Longitudinal Data with Non-ignorable Dropouts

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SUMMARY

The analysis of longitudinal dyadic data is challenging due to the complicated correlations within and between dyads, as well as possibly non-ignorable dropouts. Based on a mixed-effects hybrid model, we propose an approach to analyze longitudinal dyadic data with non-ignorable dropouts. We factorize the joint distribution of the measurement and dropout processes into three components: the marginal distribution of random effects, the conditional distribution of the dropout process given the random effects, and the conditional distribution of the measurement process given the random effects and missing data patterns. We model the conditional dropout process using a discrete survival model, and the conditional measurement process using a latent-class pattern-mixture model. These models account for the dyadic interdependence using the “actor” and “partner” effects and dyad-specific random effects. We use the latent-dropout-class approach to address the problem of a large number of missing data patterns caused by the dyadic data structure. We evaluate the performance of the proposed method using a simulation study, and apply our method to a longitudinal dyadic data set that arose from a prostate cancer trial.

Keywords

dyadic; non-ignorable missingness; mixed-effect; longitudinal; latent class

1. Introduction

Dyadic data arise when the study units are paired subjects (i.e., dyads), such as married couples, twins, and roommates. Members of dyads are inherently interdependent as they share a similar environment and influence each other’s cognitions, emotions and behaviors (Gottman et al., 2002; Cook et al., 1995). For example, if a wife is not satisfied with her marriage, her husband is also likely to have low marital satisfaction. As a result, the

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Supplementary Materials

Web Appendixes A and B, referenced in Sections 2.4 and 3, respectively, are available with this paper at the *Biometrics* website on Wiley Online Library.

observations from two members of a dyad are correlated. One important goal of a dyadic study is to understand the role of the embedded dyadic interaction and how the attributes and behaviors of one dyad member impact the outcome of the other dyad member.

Compared to conventional longitudinal data, in which study units are mutually independent individuals, the analysis of longitudinal dyadic data is more challenging. In addition to the within-subject correlation due to the repeated measures, we also need to account for the within-dyad correlation induced by the interdependence between two members within a dyad. In addition, this analysis is often further complicated by dropouts due to a prolonged study duration, and in many cases these dropouts are non-ignorable in the sense that the dropout process depends on the unobserved outcome process.

The structure of longitudinal dyadic data, in which measures are correlated both within and between longitudinal processes, is similar to that of multivariate longitudinal data (Gray and Brookmeyer, 1998; Roy and Lin, 2000, 2002). However, there are some important differences. Multivariate longitudinal data typically concern multiple outcomes measured repeatedly from the same independent subject. In contrast, longitudinal dyadic data concern the same (or similar) longitudinal outcome from two correlated subjects (within a dyad) who typically have different characteristics or covariates. As a result, the measures of multivariate longitudinal data often terminate at the same time point when a subject drops out; whereas for dyadic longitudinal data, the two longitudinal processes can terminate at different time points as two subjects of a dyad can drop out at different times.

Our research is motivated by a longitudinal dyadic study of the spousal relationship and sexual functioning of men who have received treatment for prostate cancer and their spouses (Schover et al., 2012). A common side effect of prostate cancer treatment (e.g., prostatectomy and radiation therapy) is decreasing sexual function. At long-term follow-up, the great majority of prostate cancer survivors are found to have experienced post-treatment erectile dysfunction (ED). A prospective cohort study showed that about 65% of prostate cancer survivors aged 50–54 had ED, which represents a level about 10- to 15-fold higher than their peers of the same age (Bacon et al., 2003). In addition, 50% to 55% of prostate cancer survivors reported low desire for sex (Potosky et al., 2004). A pilot study conducted at MD Anderson Cancer Center showed that a sexual-counseling-based intervention known as Counseling About Regaining Erections and Sexual Satisfaction (CAREss) could potentially improve the sexual functioning and satisfaction of men with prostate cancer and their partners (Canada et al., 2005). As an extension of that pilot study, a randomized clinical trial was initiated to compare two formats of the intervention: face-to-face or internet-based CAREss. The primary objective of the study is to compare the efficacy of the two formats of CAREss on enhancing both partners' sexual functioning, and to understand the dyadic interplay and interdependence between patients and their spouses.

In this study, a total of 124 eligible men with prostate cancer and their spouses were randomized into face-to-face or internet-based intervention arms. The important eligibility criteria included that the male patient was heterosexual, aged ≥ 18 years, and had been treated for localized prostate cancer, and that each participating couple was married or had been living together for more than one year. The minimization method of Pocock and Simon

(1975) was used to balance prognostic factors (e.g., the man's age, race, and surgery type) between the two intervention arms during randomization. As the primary endpoint, the participants' sexual functioning was measured repeatedly via questionnaires at baseline, post-intervention, and at 3-month, 6-month, and 12-month follow-ups, based on the International Index of Erectile Functioning (IIEF, Rosen et al., 2002) and the Female Sexual Function Index (FSFI, Wiegel et al., 2005). The IIEF and FSFI are 15-item questionnaire-based scales for measuring overall sexual functions for men and women, respectively, with higher values indicating better sexual function. Some example questions from the IIEF are "Over the past 4 weeks, how often were you able to get an erection during sexual activity?" and "Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?" Some example questions from the FSFI are "Over the past 4 weeks, how often did you feel sexual desire or interest?" and "Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?"

As is common for studies involving sexual functioning and related behaviors, this study suffered from a substantial number of dropouts, which was possibly related to the missing outcomes of the IIEF and FSFI, e.g., subjects with lower sexual functioning scores tend to drop out early. At baseline, 124 couples finished the questionnaire, but at the 12-month follow-up, only 35 couples remained in the study and completed the questionnaire. The number of dropouts at different time points is summarized in Table 1. Note that the two partners in a couple did not necessarily drop out at the same time. It is possible that one member of the couple dropped out early and the other member remained in the study or dropped out later.

Numerous methods have been proposed to analyze longitudinal data with non-ignorable dropouts, including selection models (Wu and Carroll, 1988; Diggle and Kenward, 1994; Follman and Wu, 1995), pattern-mixture models (Wu and Bailey, 1989; Little 1993, 1994; Hogan and Laird, 1997; Roy and Daniels, 2008), and estimation equations with inverse probability methods (Robins, Rotnitzky and Zhao 1995; Rotnitzky, Robins, and Scharfstein, 1998; Scharfstein, Rotnitzky and Robins, 1999; Farewell, 2010). Recently, Yuan and Little (2010) proposed a new class of models, called a mixed-effects hybrid model (MEHM), which combines features of selection and pattern-mixture models. The MEHMs incorporate a feature of selection models in that they directly model the dropout process, and also incorporate a feature of pattern-mixture models in that the sample is stratified by the missing data patterns and the outcome process is modeled as conditional on these patterns. Comprehensive reviews of methods handling non-ignorable dropout in longitudinal data can be found in (Little 1995, 2009), Verbeke and Molenberghs (2000), and Hogan, Roy, and Korkontzelou (2004), and Daniels and Hogan (2008).

Despite the rich body of literature on conventional longitudinal data analysis with non-ignorable dropouts, methods for handling non-ignorable dropouts in longitudinal dyadic data have been very limited. Recently, Zhang and Yuan (2010) developed a selection-model-based approach in which the dropout is assumed to directly depend on the missing values. In this article, we propose a latent-class MEHM to analyze longitudinal dyadic data with non-ignorable dropouts. The proposed method can be viewed as a generalized pattern-mixture

approach as it contains the conventional pattern-mixture model as a special case. Based on the MEHM framework, we factorize the joint distribution of the measurement and dropout processes into the marginal distribution of random effects, the conditional distribution of the dropout process given the random effects, and the conditional distribution of the measurement process given the random effects and missing data patterns. We model the conditional dropout process using a discrete survival model, and the conditional measurement process using a latent-class pattern-mixture model. As we describe later, the unique features of longitudinal dyadic data bring new modeling challenges that require a modeling strategy that is rather different from that for conventional longitudinal data.

The rest of this article is organized as follows. In Section 2, we propose the latent-class MEHM for longitudinal dyadic data with non-ignorable dropouts and describe the prior and parameter estimation based on the Markov chain Monte Carlo algorithm. We conduct a simulation study to evaluate the performance of the proposed method in Section 3, and apply our method to the prostate cancer dyadic data in Section 4. We conclude with a brief discussion in Section 5.

2. Probability model

Suppose a longitudinal dyadic study is designed to collect K repeated measurements of an outcome Y for each of n dyads. Let $\mathbf{D}_i = (D_{i1}, D_{i2})^\top$ denote the dropout times for the two members in the i th dyad. We allow two members of a dyad to drop out at different time points. Let Y_{ijk} and $\mathbf{X}_{ijk}$ denote the respective outcome and vector of the covariates of the j th member in the i th dyad at the k th measurement time, for $i = 1, \dots, n$, $j = 1, 2$, and $k = 1, \dots, K$. We denote $\mathbf{Y}_{ij} = (Y_{ij1}, \dots, Y_{ijD_{ij}})^\top$, $\mathbf{Y}_i = (\mathbf{Y}_{i1}, \mathbf{Y}_{i2})^\top$, $\mathbf{X}_{ij} = (\mathbf{X}_{ij1}, \dots, \mathbf{X}_{ijD_{ij}})^\top$ and $\mathbf{X}_i = (\mathbf{X}_{i1}, \mathbf{X}_{i2})^\top$. Let $\mathbf{b}_i = (\mathbf{b}_{i1}, \mathbf{b}_{i2})$ denote the random effects associated with two members of the i th dyad.

When dropouts are non-ignorable, we need to model the joint distribution of the outcome and dropout processes in order to obtain valid inference (Little and Rubin, 2002). Taking the approach of the MEHM, we factorize the joint distribution of $\mathbf{Y}_i$, $\mathbf{D}_i$ and $\mathbf{b}_i$, i.e., $f(\mathbf{D}_i, \mathbf{D}_{i2}, \mathbf{Y}_{i1}, \mathbf{Y}_{i2}, \mathbf{b}_{i1}, \mathbf{b}_{i2} | \mathbf{X}_i, \boldsymbol{\theta})$, into three components, as follows:

$$\begin{aligned} & f(\mathbf{D}_{i1}, \mathbf{D}_{i2}, \mathbf{Y}_{i1}, \mathbf{Y}_{i2}, \mathbf{b}_{i1}, \mathbf{b}_{i2} | \mathbf{X}_i, \boldsymbol{\theta}) \\ &= f(\mathbf{b}_{i1}, \mathbf{b}_{i2} | \mathbf{X}_i, \boldsymbol{\theta}_1) f(\mathbf{D}_{i1}, \mathbf{D}_{i2} | \mathbf{X}_i, \mathbf{b}_{i1}, \mathbf{b}_{i2}, \boldsymbol{\theta}_2) \quad (1) \\ & \times f(\mathbf{Y}_{i1}, \mathbf{Y}_{i2} | \mathbf{X}_i, \mathbf{b}_{i1}, \mathbf{b}_{i2}, \mathbf{D}_{i1}, \mathbf{D}_{i2}, \boldsymbol{\theta}_3), \end{aligned}$$

where $\boldsymbol{\theta}_1$, $\boldsymbol{\theta}_2$, and $\boldsymbol{\theta}_3$ are vectors of unknown parameters, with $\boldsymbol{\theta} = (\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \boldsymbol{\theta}_3)$. The first component specifies the marginal distribution of the random effects; the second component models the dropout process (i.e., how the dropout process depends on the random effects), a feature of (mixed-effects) selection models; and the third component models the longitudinal outcome process conditional on the missing data pattern, a feature of pattern-mixture models. The MEHM factorization provides a flexible framework in which to model the longitudinal dyadic data with non-ignorable dropouts. The MEHM becomes a pattern-mixture model if the dropout process is independent of the random effects (i.e., $f(\mathbf{D}_{i1}, \mathbf{D}_{i2} | \mathbf{X}_i, \mathbf{b}_{i1}, \mathbf{b}_{i2}, \boldsymbol{\theta}_2) = f(\mathbf{D}_{i1}, \mathbf{D}_{i2} | \mathbf{X}_i, \boldsymbol{\theta}_2)$), and becomes a shared-parameter model (SPM) if the

outcome process is independent of the dropout process after conditioning on random effects b_i . In the following, we specify each component of the MEHM factorization for longitudinal dyadic data.

2.1 Random-effects model

Random effects are routinely used to account for the within-subject correlation (due to the repeated measures) for conventional longitudinal data. For longitudinal dyadic data, in addition to the within-subject correlation, we also need to account for the within-dyad correlation. For notational simplicity, we focus on the case of one random intercept and one random slope. The extension to more than two random effects is straightforward. Let b_{ij0} and $b_{ij1}, j = 1, 2$, denote the random intercept and slope for the j th member of the i th dyad and $\mathbf{b}_{ij} = (b_{ij0}, b_{ij1})^\top$. We model the random effects distribution $f(\mathbf{b}_{i1}, \mathbf{b}_{i2} | \mathbf{X}_i, \boldsymbol{\theta}_1)$ in (1) as a multivariate normal distribution of the form

$$\begin{pmatrix} b_{i10} \\ b_{i11} \\ b_{i20} \\ b_{i21} \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \nu_1^2 & \nu_1\nu_2\rho_1 & \nu_1\nu_3\rho_2 & \nu_1\nu_4\rho_3 \\ \nu_1\nu_2\rho_1 & \nu_2^2 & \nu_2\nu_3\rho_4 & \nu_2\nu_4\rho_5 \\ \nu_1\nu_3\rho_2 & \nu_2\nu_3\rho_4 & \nu_3^2 & \nu_3\nu_4\rho_6 \\ \nu_1\nu_4\rho_3 & \nu_2\nu_4\rho_5 & \nu_3\nu_4\rho_6 & \nu_4^2 \end{pmatrix} \right), \quad (2)$$

in which $\nu_1\nu_3\rho_2$ and $\nu_2\nu_4\rho_5$ capture the correlations of the random intercepts and slopes, respectively, between two members of a dyad; and $\nu_1\nu_2\rho_1$ and $\nu_2\nu_4\rho_6$ capture the correlations between the random intercepts and slopes within the first and second members, respectively. In a more general form, we can allow the ν 's and ρ 's to depend on covariates $\mathbf{X}_i$. For example, when analyzing the prostate cancer data in Section 4, we allow the subjects in the two intervention arms to have two separate sets of variance and correlation parameters.

2.2 Dropout model

When modeling the dropout process $f(D_{i1}, D_{i2} | \mathbf{X}_i, \mathbf{b}_{i1}, \mathbf{b}_{i2}, \boldsymbol{\theta}_2)$, we should take into account two unique features of dyadic data. The first one is that the probabilities of dropout are correlated between two members of a dyad, i.e., if one member has a high/low propensity to drop out, the other member also tends to have a high/low propensity to drop out. The second feature is that, in many practical cases, the dropout of one member accelerates the dropout of the other member. For example, when study subjects are married couples, given that the wife has dropped out of the study, her husband often drops out very soon afterward. We model the dropout processes of two members of dyads using the discrete time survival model (Agresti, 2002). We account for the first feature by introducing a common frailty (or random effect) shared by the survival models of the two members; and account for the second feature by including as a covariate the indicator variable of whether the other member has dropped out.

Specifically, let $\lambda_{ijk} = \Pr(D_{ij} = k | D_{ij} \neq k, \mathbf{X}_{ij}, \mathbf{b}_{ij})$ for $k = 1, \dots, K$ denote the hazard of dropout for the j th member in the i th dyad at the k th measurement time, and $I(\cdot)$ denote an indicator function. The discrete time survival models for two members of dyads are given by

$$\begin{aligned}\text{logit}(\lambda_{i1k}) &= d_i + \eta_{01} + \mathbf{X}_{i1k}\boldsymbol{\eta}_1 + \mathbf{X}_{i2k}\tilde{\boldsymbol{\eta}}_1 + \mathbf{b}_{i1}^\top \boldsymbol{\zeta}_1 + \kappa_1 I(D_{i2} \leq k), \\ \text{logit}(\lambda_{i2k}) &= d_i + \eta_{02} + \mathbf{X}_{i2k}\boldsymbol{\eta}_2 + \mathbf{X}_{i1k}\tilde{\boldsymbol{\eta}}_2 + \mathbf{b}_{i2}^\top \boldsymbol{\zeta}_2 + \kappa_2 I(D_{i1} \leq k), \\ d_i &\sim N(0, \varpi^2),\end{aligned}\quad (3)$$

where d_i is a dyad-specific random effect (or propensity to dropout) accounting for the correlation between members within a dyad, and $\boldsymbol{\zeta}_1$ and $\boldsymbol{\zeta}_2$ describe how dropout depends on the respective random effects $\mathbf{b}_{i1}$ and $\mathbf{b}_{i2}$. In this model, covariate effects $\boldsymbol{\eta}_1$, $\tilde{\boldsymbol{\eta}}_1$, $\boldsymbol{\eta}_2$ and $\tilde{\boldsymbol{\eta}}_2$ have intuitive interpretations similar to those of the “actor–partner” interdependence model, a conceptual framework proposed by Cook and Kenny (2005) to study dyadic relationships in the social sciences and behavioral research fields. Specifically, $\boldsymbol{\eta}_1$ represents the “actor” effects of the patient, which describe how the covariates of the patient affect his own dropout process, and $\tilde{\boldsymbol{\eta}}_1$ represents the “partner” effects for the patient, which describe how the covariates from the spouse affect the dropout of the patient. Similarly, $\boldsymbol{\eta}_2$ and $\tilde{\boldsymbol{\eta}}_2$ characterize the “actor” effects and the “partner” effects for the dropout of the spouse. These “actor” and “partner” effects provide important information about the interdependence within dyads. In model (3), the acceleration parameters κ_1 and κ_2 capture another aspect of the within-dyad interdependence: these two parameters represent the extra hazard of dropout induced by the dropout of one of the dyadic members. The likelihood of a participant having dropped out at the k th measurement time is given by

$$\Pr(D_{ij}=k) \begin{cases} \lambda_{ijk} \prod_{l=1}^{k-1} (1 - \lambda_{ijl}), & k < K, \\ \prod_{l=1}^K (1 - \lambda_{ijl}), & k = K, \end{cases} \quad (4)$$

where $k = K$ indicates the case that the participant completes all follow-up assessments.

2.3 Outcome model

Our outcome model $f(\mathbf{Y}_{i1}, \mathbf{Y}_{i2} | \mathbf{X}_i, \mathbf{b}_{i1}, \mathbf{b}_{i2}, D_{i1}, D_{i2}, \boldsymbol{\theta}_3)$ takes a form similar to that of the pattern-mixture model (PMM), in which the outcome processes $\mathbf{Y}_{i1}$ and $\mathbf{Y}_{i2}$ are modeled conditional on the missing data pattern determined by D_{i1} and D_{i2} . For conventional longitudinal data with independent subjects, the missing data pattern is typically formed according to the dropout time. For example, in the case of K measurement times, there would be a total of K possible missing data patterns, each one corresponding to a dropout time. A natural extension of this approach to the longitudinal dyadic data is to form the dropout pattern based on the paired dropout times of dyads (D_{i1}, D_{i2}) , since in this case the independent units are dyads. Unfortunately, such an approach often results in a large number of missing data patterns. As each D_{i1} and D_{i2} can take K possible values, there are a total of K^2 possible missing data patterns. For instance, a moderate value of $K = 5$ leads to 25 possible missing data patterns. Given the large number of missing data patterns, the number of observations within the patterns can be sparse, resulting in unstable estimates and a nonidentification problem. To address this issue, we adopt the latent-dropout–class approach of Roy (2003) and Roy and Daniels (2008). Rather than assuming that the dropout pattern is deterministically defined by the dropout times, we assume that there exists a small number of M latent dropout classes with $M < K^2$. Class membership is unobserved, but the probability of being in a particular latent dropout class is determined by the dropout time. In other words, we “group” the dropout times into M classes. We will discuss how to determine

the value of M later. In the following, we first describe a model linking the latent class membership with the observed dropout times, and then specify an outcome model conditional on the latent class.

Let $\mathbf{S}_i = (S_{i1}, \dots, S_{iM})^\top$ be a vector of indicators such that $S_{im} = 1$ if the i th dyad belongs to class m or $S_{im} = 0$ otherwise. We assume that the probability of the i th dyad belonging to the m th latent class follows a proportional odds model:

$$\text{logit} \left\{ \text{pr} \left(\sum_{m=1}^l S_{im} = 1 \mid D_{i1}, D_{i2} \right) \right\} = \tau_{0l} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2}, l = 1, \dots, M-1, \quad (5)$$

where $\tau_{01} \dots \tau_{0M-1}$ and τ_1, τ_2 , and τ_3 are unknown parameters. Under this model, S_{im} follows a multinomial distribution with probability parameters $p_{im} = \text{pr}(S_{im} = 1 \mid D_{i1}, D_{i2})$, $m = 1, \dots, M$, which are given by

$$\begin{aligned} p_{i1} &= \frac{\exp(\tau_{01} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2})}{1 + \exp(\tau_{01} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2})}, 1 < m < M, p_{im} \\ &= \frac{\exp(\tau_{0m} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2})}{1 + \exp(\tau_{0m} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2})} \\ &\quad - \frac{\exp(\tau_{0m-1} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2})}{1 + \exp(\tau_{0m-1} + \tau_1 D_{i1} + \tau_2 D_{i2} + \tau_3 D_{i1} D_{i2})}, p_{iM} \\ &= 1 - \sum_{m=1}^{M-1} p_{im}. \end{aligned}$$

Assuming that conditional on the latent class membership $\mathbf{S}_i$, $\mathbf{Y}_{i1}$ and $\mathbf{Y}_{i2}$ are independent of $\mathbf{D}_i$, we model the outcome process using the following mixed-effects model:

$$\begin{aligned} Y_{i1k} \mid \mathbf{X}_i, \mathbf{Z}_i, \mathbf{b}_i, S_{im} = 1 &\sim N(\alpha_1^{(m)} + \mathbf{Z}_{i1k} \mathbf{b}_{i1} + \mathbf{X}_{i1k} \boldsymbol{\beta}_1^{(m)} + \mathbf{X}_{i2k} \tilde{\boldsymbol{\beta}}_1^{(m)}, \sigma_1^{(m)}), \\ Y_{i2k} \mid \mathbf{X}_i, \mathbf{Z}_i, \mathbf{b}_i, S_{im} = 1 &\sim N(\alpha_2^{(m)} + \mathbf{Z}_{i2k} \mathbf{b}_{i2} + \mathbf{X}_{i2k} \boldsymbol{\beta}_2^{(m)} + \mathbf{X}_{i1k} \tilde{\boldsymbol{\beta}}_2^{(m)}, \sigma_2^{(m)}), \end{aligned} \quad (6)$$

where $\mathbf{Z}_{i1k}$ and $\mathbf{Z}_{i2k}$ are vectors of covariates associated with the respective random effects $\mathbf{b}_{i1}$ and $\mathbf{b}_{i2}$. In this model, $\boldsymbol{\beta}_1^{(m)}$ represents the “actor” effects of the patient, which describe how the covariates of the patient affect his current outcome within the latent (missing data pattern) class m ; and $\tilde{\boldsymbol{\beta}}_1^{(m)}$ represents the “partner” effects for the patient, which describe how the covariates from the spouse affect the outcome of the patient, conditional on the latent class m . Similarly, $\boldsymbol{\beta}_2^{(m)}$ and $\tilde{\boldsymbol{\beta}}_2^{(m)}$ characterize the respective “actor” effects and “partner” effects for the spouse of the patient within the latent class m . These “actor” and “partner” effects reflect the interdependence within dyads. For the covariance matrices, we assume that, conditional on random effects $\mathbf{b}_i$ and latent class S_{im} , regression errors are independent, but allow the variance of the errors (i.e., $\sigma_1^{(m)}$ and $\sigma_2^{(m)}$) to vary across both dyadic members and the latent class. A more parsimonious specification is to assume that the variance is different between dyadic members but invariant to the latent class, that is, $\sigma_1^{(m)} = \sigma_1$ and $\sigma_2^{(m)} = \sigma_2$. Note that when both the regression coefficients and variances are

invariant to the latent class (or equivalently, there is only one latent class), the proposed model becomes the SPM.

The above latent-class pattern-mixture model specifies the conditional covariate effects given the latent class of missing data patterns. In practice, we are often interested in the marginal covariate effects, which can be obtained by averaging over the latent class. For example, the marginal “actor” effects of X_{i1} , say β_1 , can be obtained as follows,

$$\beta_1 = \sum_{m=1}^M \beta_1^{(m)} \text{pr}(S_{im}=1), \quad (7)$$

where

$$\text{pr}(S_{im}=1) = \int \int \text{pr}(S_{im}=1 | D_{1i}, D_{2i}) P(D_{1i}, D_{2i}) dD_{1i} dD_{2i}.$$

We now discuss how to choose the number of latent classes M . We choose the value of M so that the corresponding model has the best goodness-of-fit according to a certain model-fit statistic, such as the deviance information criterion (DIC) (Spiegelhalter et al., 2002). In principle, this can be done by fitting the model for each value of M between 1 and $K \times K$, and finding the one yielding the smallest value of DIC. However, in practice, as the main purpose of using the latent dropout class is to obtain a parsimonious model, we can limit such a search within a narrower range, for example $M \leq K$. Alternatively, starting from $M = 1$, we progressively increase the value of M until the DIC first starts to increase, and then select the value of M that yields the smallest DIC as the number of latent classes.

2.4 Prior and posterior estimation

We fit the proposed latent-class MEHM using a Markov chain Monte Carlo (MCMC) algorithm. We adopted independent vague priors for the model parameters as follows,

$$\begin{aligned} \nu_{jk}^2 &\stackrel{iid}{\sim} IG(a_\nu, b_\nu), j=1, 2, k=0, 1, \\ \varpi^2 &\stackrel{iid}{\sim} IG(a_\varpi, b_\varpi), \\ \rho_0, \rho_1 &\stackrel{iid}{\sim} Unif(-1, 1), \\ \eta_{01}, \boldsymbol{\eta}_1, \tilde{\eta}_1, \eta_{02}, \boldsymbol{\eta}_2, \tilde{\eta}_2, \boldsymbol{\zeta}_1, \boldsymbol{\zeta}_2, \kappa_1, \kappa_1 &\stackrel{iid}{\sim} N(0, c^{-1}), \\ \alpha_1, \alpha_2, \boldsymbol{\beta}_1^{(m)}, \tilde{\boldsymbol{\beta}}_1^{(m)}, \boldsymbol{\beta}_2^{(m)}, \tilde{\boldsymbol{\beta}}_2^{(m)} &\stackrel{iid}{\sim} N(0, c^{-1}), \\ \tau_1, \tau_2, \tau_3 &\stackrel{iid}{\sim} N(0, c^{-1}), \\ (\tau_{01}, \tau_{02}, \dots, \tau_{0M-1}) &\sim N_{M-1}(\mathbf{0}, c^{-1}\mathbf{I}) \times I(\tau_{01} < \tau_{02} < \dots < \tau_{0M-1}), \\ \sigma_j^{(m)} &\stackrel{iid}{\sim} IG(a_\sigma, b_\sigma), m=1, \dots, M, \end{aligned}$$

where $N_{M-1}(\mathbf{0}, c^{-1}\mathbf{I})$ denotes a $(M-1)$ -variate normal distribution with mean 0 and covariance matrix $c^{-1}\mathbf{I}$, $IG(a, b)$ represents the inverse gamma distribution with a shape parameter a and a scale parameter b , and $Unif(0, 1)$ denotes a uniform distribution with the support $[0, 1]$. For all inverse-gamma priors specified above, we set both shape and scale parameters at 0.1 to make the prior vague; and for normal priors, we set the precision $c = 10^{-6}$ to minimize the influence of the prior. The order restriction on the parameter τ_0 is

abided by the indicator function of this order constraint. We employ the Gibbs sampler (Geman and Geman, 1984) as the posterior sampling strategy, details of which can be found in Web Appendix A.

3. Simulation study

We conducted a simulation study to evaluate the performance of the proposed method, with $n = 300$ dyads and $K = 4$ repeated measurements. We first simulated the random effects b_{ij0} and b_{ij1} , $j = 1, 2$, based on model (2) with variances $\nu_1^2 = \nu_2^2 = \nu_3^2 = \nu_4^2 = 1$ and correlation coefficients $\rho_2 = \rho_5 = 0.5$ and $\rho_1 = \rho_3 = \rho_4 = \rho_6 = 0$.

Conditional on the random effects, we then simulated the dropout time for two members of the i th dyad based on the hazards $\text{logit}(\lambda_{i1k}|\mathbf{b}, X) = d_i + 1.5 - 2.5X_{i1k} + 0.5b_{i10} + 0.5b_{i11} + I(D_{i2} = k)$ and $\text{logit}(\lambda_{i2k}|\mathbf{b}, X) = d_i + 1.5 - 2.5X_{i2k} + 0.5b_{i20} + 0.5b_{i21} + I(D_{i1} = k)$, respectively, where random effects $d_i \sim N(0, 1)$ and covariate $X_{ijk} \sim N(1, 1)$ for $j = 1, 2$. Under this dropout process, on average, about 45% of the participants dropped out at the second follow-up visit (37% of member 1 participants and 53% of member 2 participants), about 14% of the participants dropped out at the third follow-up visit (15% of member 1 participants and 12% of member 2 participants), and 7% of the participants dropped out at the final follow-up visit (7% of member 1 participants and 6% of member 2 participants).

We assumed that there were M latent dropout classes and they were related to the dropout time according to model (5). Within each latent dropout class, the outcome variable Y was generated according to the following models,

$$Y_{i1k}|\mathbf{X}_i, Z_{ik}, \mathbf{b}_{i1}, S_{im}=1 \sim N(\alpha_1^{(m)} + Z_{ik}\mathbf{b}_{i1} + X_{i1k}\beta_1^{(m)} + X_{i2k}\tilde{\beta}_1^{(m)}, \sigma_1^{(m)}),$$

$$Y_{i2k}|\mathbf{X}_i, Z_{ik}, \mathbf{b}_{i2}, S_{im}=1 \sim N(\alpha_2^{(m)} + Z_{ik}\mathbf{b}_{i2} + X_{i2k}\beta_2^{(m)} + X_{i1k}\tilde{\beta}_2^{(m)}, \sigma_2^{(m)}),$$

where $Z_{ik} = (1, k)$ denotes the unit and the measurement time corresponding to the random intercept and random slope. We considered four simulation settings that differ in the missing data mechanism: (I) the number of latent dropout classes was four, i.e., $M = 4$; (II) the number of latent dropout classes was one (i.e., $M = 1$), under which the shared parameter model (SPM) was correctly specified; (III) the dropout process was independent of random effects by setting $\zeta_1 = \zeta_2 = 0$ in model (3), under which the latent-class pattern-mixture model (PMM) was correctly specified; and (IV) the dropout was missing at random or ignorable, for which we simulated the dropout time based on the hazard $\text{logit}(\lambda_{ijk}|\mathbf{b}, X) = -1.5$, $j = 1, 2$ (i.e., the dropout times are independent of unobserved random effects) and also assumed that outcome Y was independent of the missing data pattern. The values of the simulation parameters for each of the simulation settings can be found in Web Appendix B. We compared the proposed latent-class mixed-effects hybrid model (MEHM) to the standard random-effects model (REM; Laird and Ware, 1982), SPM and PMM, based on 500 simulation replicates.

Table 2 displays the relative bias (i.e., the bias divided by the true value of the parameter), mean squared error (MSE), and coverage probability of the 95% credible (or confidence)

interval for the marginal parameter (or effect) estimates under the four methods. When there were four latent classes, the proposed MEHM outperformed the three other methods and yielded unbiased estimates and sound coverage rates close to the nominal value. The REM and SPM performed poorly with large biases and coverage rates generally under 50%. Compared to the REM and SPM, the PMM had less bias, but its coverage rate was still under the nominal value, mostly lower than 90%. When there was one latent class, under which the SPM was correctly specified, the SPM, PMM and MEHM performed similarly well, with minimal bias and reasonable coverage rates. The REM performed poorly because it failed to take into account the non-ignorable missing data mechanism. For example, the coverage rate for β_2 under the REM was only 68%. When the dropout was independent of random effects, the PMM and MEHM were the best, yielding unbiased estimates and coverage rates close to the nominal value; whereas the REM and SPM led to poor performances and had coverage rates that were all lower than 50%. When the dropouts were missing at random, all methods performed well.

4. Application

We applied the proposed method to the prostate cancer dyadic data. The primary endpoints are the IIEF (for patients) and FSFI (for spouses) scores (i.e., sexual functioning and satisfaction) measured at a post-treatment visit and at 3-month, 6-month, and 12-month follow-up visits, where improvements in IIEF and FSFI represent better sexual function/satisfaction. We considered a random intercept and slope and specified their joint distribution as model (2). The random slope is associated with the measurement time to allow each subject to have an individual trajectory. We found that the unstructured covariance matrix (with six correlation parameters) appeared to have identification issues (i.e., the MCMC failed to converge), and thus adopted a parsimonious covariance matrix that models the correlations of the random effects between the two members of a dyad (i.e., ρ_2 and ρ_5), while setting the other pairwise correlations at zero (i.e., $\rho_1 = \rho_3 = \rho_4 = \rho_6 = 0$). We allowed the covariance matrix to depend on the intervention by specifying a separate set of correlation and variance parameters for each of the two intervention arms. In this analysis, we used subscript $j = 1$ to indicate the patient and 2 to indicate the spouse.

In the dropout and measurement models, we considered seven fixed-effects covariates (i.e., X_{i1k} and X_{i2k}): measurement time, the respective levels of relationship satisfaction and psychological distress for the patient and his spouse, an intervention indicator (with 0 indicating the face-to-face intervention arm and 1 indicating the internet-based intervention arm), and the baseline measurement of IIEF or FSFI. The levels of relationship satisfaction for both the patient and his spouse were measured by a six-item questionnaire-based scale called the abbreviated Spanier Dyadic Adjustment Scale (A-DAS, Sharpley and Rogers, 1984) with larger values representing stronger relationships. The individual levels of psychological distress for the patient and his spouse were measured by an 18-item questionnaire-based scale called the Brief Symptom Inventory (BSI, Zabora, et al., 2001) with larger values representing higher distress levels. The A-DAS and BSI used in the analysis were baseline measures; Table S1 in Web-based Supplementary Materials provides the summary statistics of these measures and also the IIEF and FSFI.

To determine the number of latent classes, beginning from one class, we increased the number of classes until the DIC increased. The DICs for the models with one, two and three latent classes were 6691.3, 6621.2 and 6778.3, respectively, and thus we used the two-class model for our analysis. When fitting the model, we used 50,000 iterations for the burn-in, and collected 10,000 posterior samples for inference. We thinned the posterior samples by every tenth iteration.

Table 3 shows the parameter estimates for the random effects under the SPM, PMM, and the proposed MEHM. Despite some minor variations, all three methods suggested that the random intercepts and slopes of the patient and spouse were positively correlated, as the estimates of the correlation coefficients ρ_2 and ρ_5 were significantly larger than 0 in both the face-to-face and internet-based intervention arms. Table 4 reports the parameter estimates for the dropout model under the SPM and the proposed MEHM (the PMM does not require modeling the dropout process). Both approaches indicated strong acceleration effects on dropouts between the patient and spouse, i.e., the dropout of a patient (or spouse) significantly accelerated the dropout of his (or her) spouse, as reflected by the large positive estimates of κ_1 and κ_2 . This result suggests that, if interested in improving participant adherence to the study, we can achieve a better adherence rate by treating the dyad as the intervention unit and using interventions that target both the patient and spouse. In addition, we also found that the baseline IIEF (or FSFI) measure was significantly associated with the dropout process for the patient (or spouse). Patients (or spouses) with lower baseline IIEF (or FSFI) scores were more likely to drop out early.

Table 5 displays estimates of the outcome model under the MEHM, REM, SPM, and PMM. Under the proposed MEHM, the A-DAS score (i.e., the relationship satisfaction) showed a significant “actor” effect on sexual functioning (i.e., IIEF/FSFI score) for both the patient and spouse. The posterior estimate of this “actor” effect was 1.26 (with 95% credible interval = [0.17, 2.91]) for the patient and 0.72 (with 95% credible interval = [0.25, 1.29]) for the spouse, suggesting that the marital relationship satisfaction had a stronger positive effect for men’s sexual functioning than women’s. In contrast, the “partner” effect of the A-DAS score was not statistically significant for both the patient and spouse, suggesting that sexual functioning was mainly affected by the participant’s own sense of relationship satisfaction, not his/her spouse’s. As for the treatment effect, we did not detect a significant difference between the two intervention groups. The 95% credible interval of the treatment effect contained zero, suggesting that the two formats of the CAREss intervention were comparably efficacious. Since the internet-based CAREss is more convenient and less costly to administer, in practice we may prefer to deliver the CAREss intervention through the internet rather than by face-to-face counseling.

The REM yielded results similar to those of the proposed model, that is, the A-DAS score had a significant “actor” effect but insignificant “partner” effect, and there was no significant difference between the two intervention groups. However, the estimates from the REM are smaller than those from the proposed method. For example, the estimate of the “actor” effect of the A-DAS score for patients was 1.26 under the proposed method and 0.77 under the REM; and the estimate of the treatment effect was 1.58 under the proposed method and -0.82 under the REM. Compared to the MEHM, the SPM failed to detect a

significant “actor” effect of the A-DAS score for the patient, with the 95% credible interval containing zero. The PMM yielded results similar to those of the MEHM because in the latter model the estimates of ζ_{10} , ζ_{11} , ζ_{20} , ζ_{21} were rather close to 0 (see Table 4). When the ζ 's equal 0 (i.e., the dropout process is independent of random effects), the MEHM is equivalent to the PMM.

An important assumption underlying the proposed latent-class MEHM is that the outcome Y_{ijk} is independent of the dropout times D_{ij} given the dropout latent class S_{im} , as stated in (6). We assessed this conditional independence assumption as follows: we first fit the proposed model by adding the D_{ij} as a regressor without the latent-class structure (i.e., without being conditional on S_{im}). The dropout time D_{ij} was significantly associated with Y_{ijk} with p-values of 0.094 and 0.002 for the patient and spouse, respectively. Then, we fit the model with the latent-class structure (i.e., conditional on S_{im}), and the associations between Y_{ijk} and D_{ij} were not significant, with p-values of 0.322 and 0.118. Such a change provides empirical evidence to support the conditional independence assumption, i.e., given S_{im} , Y_{ijk} is independent of D_{ij} .

Lastly, we assessed the goodness-of-fit for the MEHM using posterior predictive checks based on the χ^2 discrepancy measure (Gelman, Meng and Stern, 1996) as follows,

$$T(\mathbf{y}, \boldsymbol{\theta}) = \sum_i^n \sum_j^2 \sum_k^{D_{ij}} \frac{\{y_{ijk} - E(y_{ijk}|\boldsymbol{\theta})\}^2}{Var(y_{ijk}|\boldsymbol{\theta})},$$

where $\boldsymbol{\theta}$ is the collection of the model parameters. We simulated the data replicate $\mathbf{y}^{rep,l}$ from its predictive distribution for each posterior sample of $\boldsymbol{\theta}$, say $\boldsymbol{\theta}^l$, obtained from the MCMC algorithm, and then estimated the posterior predictive probability as the proportion of simulations for which $T(\mathbf{y}^{rep,l}, \boldsymbol{\theta}^l)$ equals or exceeds its realized value $T(\mathbf{y}, \boldsymbol{\theta}^l)$. The posterior predictive probability was 0.485, suggesting that the proposed model provides a good fit for the prostate cancer data. We also conducted a graphical posterior predictive check based on the Bayesian residual plot (Gelman et al., 2004). As shown in Figure 1, the average prediction errors were relatively small, around zero, without any consistent patterns, which further supports the adequacy of the proposed model.

5. Conclusion

We have proposed a latent-class mixed-effects hybrid model (MEHM) to analyze longitudinal dyadic data with non-ignorable dropouts. Based on the MEHM framework, we factorize the joint distribution of the measurement and dropout processes into the marginal distribution of the random effects, the conditional distribution of the dropout process given the random effects, and the conditional distribution of the measurement process given the random effects and missing data patterns. We model the conditional dropout process using a discrete survival model, in which the “actor” and “partner” effects are introduced to explain the dyadic interdependence, and the acceleration parameter is used to capture the fact that the dropout of one dyadic member often accelerates the dropout of the other member. We model the conditional measurement process using a latent-class pattern-mixture model, in

which we bypass the problem of a large number of dyadic dropout patterns by imposing the latent-dropout–class structure. A simulation study suggests that the proposed method yields minimal bias in the presence of non-ignorable dropouts.

In our approach, we treat the number of latent classes as a fixed value and select that value based on the DIC. As pointed out in Roy and Daniels (2008), it may be more desirable to regard the number of latent classes as an unknown parameter and estimate it jointly with the other model parameters. Under the Bayesian framework, the reversible jump Markov chain Monte Carlo method can be used for this joint estimation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Bayesian residual plots of average residuals versus average expected values for the IIEF and FSFI.

Table 1

The number of dropouts at different time points.

Dropout times for the prostate cancer survivors					
	Baseline	Post-treatment	3 months	6 months	One year
Baseline	4	6	4	1	4
Post-treatment	6	12	1	2	2
Spouse's dropout time	4	1	9	2	1
3 months	4	2	2	10	3
6 months	4	4	0	4	35
One year	1	4	0	4	35

Table 2

Simulation results, including the relative bias, mean squared error (MSE), and average coverage probability of the 95% credible (or confidence) interval for marginal parameter estimates under the standard random-effects model (REM), shared parameter model (SPM), pattern-mixture model (PMM), and the proposed latent-class mixed-effect hybrid model (MEHM).

Model		α_1	β_1	β_1^*	α_2	β_2	β_2^*
Four latent classes							
MEHM	Relative bias	0.03	0.00	0.01	-0.02	0.01	-0.02
	MSE	0.02	0.02	0.01	0.01	0.01	0.01
	Coverage	0.93	0.91	0.96	0.92	0.94	0.94
REM	% bias	0.90	0.61	0.11	-0.42	0.10	-0.46
	MSE	0.58	0.33	0.08	0.14	0.06	0.18
	Coverage	0.16	0.42	0.52	0.17	0.56	0.20
SPM	% bias	0.62	0.82	0.11	-0.34	0.17	-0.46
	MSE	0.38	0.64	0.07	0.13	0.16	0.22
	Coverage	0.21	0.11	0.43	0.19	0.28	0.14
PMM	% bias	0.06	0.08	0.01	-0.03	0.03	0.01
	MSE	0.01	0.02	0.00	0.00	0.01	0.00
	Coverage	0.83	0.83	0.90	0.84	0.72	0.93
One latent class							
MEHM	Relative bias	0.01	0.00	0.01	0.00	0.01	-0.02
	MSE	0.01	0.01	0.00	0.00	0.00	0.00
	Coverage	0.96	0.95	0.94	0.95	0.95	0.93
REM	Relative bias	0.12	0.11	0.01	-0.03	0.08	-0.05
	MSE	0.01	0.02	0.00	0.00	0.02	0.00
	Coverage	0.93	0.92	0.94	0.93	0.68	0.90
SPM	Relative bias	0.03	0.02	0.00	-0.01	0.01	-0.02
	MSE	0.01	0.01	0.00	0.00	0.00	0.01
	Coverage	0.92	0.93	0.94	0.93	0.93	0.93
PMM	Relative bias	0.02	0.01	0.02	0.00	0.01	-0.02
	MSE	0.01	0.01	0.00	0.00	0.00	0.00
	Coverage	0.96	0.96	0.93	0.96	0.96	0.95

Model	σ_1	β_1	$\tilde{\beta}_1$	σ_2	β_2	$\tilde{\beta}_2$
Dropout independent of random effects						
MEHM	Relative bias	0.02	0.01	0.01	-0.02	-0.02
	MSE	0.01	0.02	0.01	0.01	0.01
	Coverage	0.92	0.93	0.96	0.93	0.94
REM	Relative bias	0.88	0.89	0.11	-0.45	-0.49
	MSE	0.55	0.56	0.07	0.16	0.17
	Coverage	0.18	0.17	0.48	0.14	0.12
SPM	Relative bias	0.87	0.87	0.11	-0.45	-0.46
	MSE	0.53	0.53	0.07	0.15	0.16
	Coverage	0.13	0.18	0.43	0.13	0.13
PMM	Relative bias	0.02	0.02	0.01	0.01	-0.01
	MSE	0.01	0.02	0.01	0.00	0.00
	Coverage	0.92	0.94	0.92	0.94	0.95
Missing at random						
MEHM	Relative bias	0.02	0.01	0.02	-0.01	-0.02
	MSE	0.01	0.01	0.01	0.00	0.00
	Coverage	0.93	0.94	0.95	0.93	0.93
REM	Relative bias	0.02	0.02	0.02	-0.03	-0.03
	MSE	0.01	0.01	0.00	0.00	0.00
	Coverage	0.96	0.98	0.92	0.96	0.92
SPM	Relative bias	0.02	0.01	0.00	-0.02	-0.01
	MSE	0.01	0.02	0.00	0.01	0.00
	Coverage	0.94	0.92	0.94	0.93	0.93
PMM	Relative bias	0.02	0.02	0.01	-0.02	-0.04
	MSE	0.01	0.01	0.00	0.00	0.00
	Coverage	0.97	0.97	0.93	0.96	0.93

Table 3

Parameter estimates and 95% credible intervals (shown in parentheses) for the random-effects processes under the MEHM, SPM and PMM.

Treatment	Parameter	MEHM	SPM	PMM
Face-to-Face	ρ_2	0.67 (0.47, 0.88)	0.62 (0.25, 0.87)	0.66 (0.29, 0.89)
	ρ_5	0.63 (0.26, 0.91)	0.61 (0.05, 0.85)	0.60 (0.09, 0.86)
	v_1	1.49 (1.00, 2.01)	1.54 (0.98, 2.17)	1.42 (0.92, 1.96)
	v_2	1.31 (0.88, 1.85)	1.44 (0.79, 1.97)	1.22 (0.77, 1.78)
	v_3	1.45 (1.02, 2.01)	1.27 (0.90, 1.67)	1.45 (0.93, 2.04)
	v_4	1.37 (0.77, 2.05)	1.09 (0.75, 1.45)	1.35 (0.82, 2.09)
Internet-based	ρ_2	0.56 (0.11, 0.88)	0.61 (0.16, 0.91)	0.60 (0.22, 0.88)
	ρ_5	0.59 (0.09, 0.86)	0.55 (0.07, 0.83)	0.55 (0.11, 0.88)
	v_1	1.29 (0.77, 1.86)	1.22 (0.85, 1.57)	1.14 (0.63, 1.65)
	v_2	1.27 (0.60, 2.28)	1.19 (0.60, 2.36)	1.38 (0.56, 2.96)
	v_3	1.23 (0.77, 1.76)	1.16 (0.73, 1.59)	1.11 (0.68, 1.61)
	v_4	1.11 (0.50, 1.87)	1.17 (0.65, 2.03)	1.49 (0.68, 3.43)

Table 4

Parameter estimates and 95% credible intervals (shown in parentheses) for the dropout processes under the MEHM and SPM.

Covariate		MEHM	SPM
Patient	Intercept	-1.68 (-2.91, -0.40)	-1.85 (-2.97, -0.36)
	Time	0.10 (-0.31, 0.46)	0.10 (-0.33, 0.56)
	Patient A-DAS	0.00 (-0.05, 0.05)	0.01 (-0.03, 0.06)
	Patient BSI	-0.03 (-0.12, 0.06)	-0.03 (-0.11, 0.06)
	Spouse A-DAS	-0.02 (-0.06, 0.03)	-0.02 (-0.07, 0.02)
	Spouse BSI	-0.03 (-0.10, 0.04)	-0.03 (-0.09, 0.04)
	Treatment	0.03 (-0.85, 0.82)	-0.03 (-0.90, 0.96)
	Baseline	-0.04 (-0.07, -0.01)	-0.04 (-0.07, -0.01)
	ζ_{10}	0.02 (-0.22, 0.30)	-0.01 (-0.34, 0.22)
	ζ_{11}	0.02 (-0.27, 0.34)	0.04 (-0.25, 0.49)
	κ_1	3.94 (3.05, 4.94)	3.98 (2.96, 5.05)
Spouse	Intercept	-2.89 (-4.54, -1.02)	-2.65 (-3.90, -1.43)
	Time	0.06 (-0.39, 0.48)	0.05 (-0.38, 0.47)
	Spouse A-DAS	0.06 (0.01, 0.11)	0.06 (0.00, 0.11)
	Spouse BSI	0.04 (-0.02, 0.10)	0.04 (-0.02, 0.12)
	Patient A-DAS	-0.07 (-0.12, -0.03)	-0.07 (-0.12, 0.00)
	Patient BSI	-0.01 (-0.10, 0.07)	-0.02 (-0.11, 0.06)
	Treatment	0.94 (-0.12, 1.95)	0.71 (-0.05, 1.60)
	Baseline	-0.10 (-0.15, -0.05)	-0.10 (-0.15, -0.06)
	ζ_{20}	-0.01 (-0.29, 0.22)	0.00 (-0.29, 0.27)
	ζ_{21}	-0.02 (-0.31, 0.26)	0.00 (-0.35, 0.37)
	κ_2	3.58 (2.71, 4.47)	3.78 (2.94, 4.68)

Table 5

Parameter estimates and 95% confidence/credible intervals (shown in parentheses) for the outcome processes of patient and spouse based on the MEHM, REM, SPM and PMM.

Covariate	MEHM	REM	SPM	PMM
Patient				
Intercept	-1.24 (-48.29, 51.82)	6.12 (-7.89, 20.13)	0.89 (-38.04, 35.64)	-5.83 (-40.93, 33.26)
Time	0.14 (-1.12, 1.69)	0.43 (-1.52, 2.39)	0.02 (-1.42, 1.50)	0.45 (-0.92, 1.90)
Pateint A-DAS	1.26 (0.17, 2.91)	0.77 (0.25, 1.28)	1.19 (-0.04, 2.08)	1.32 (0.36, 2.42)
Patient BSI	0.00 (-0.62, 0.63)	-0.20 (-0.59, 0.19)	-0.03 (-0.56, 0.45)	0.05 (-0.37, 0.41)
Spouse A-DAS	0.17 (-0.64, 1.15)	-0.26 (-0.54, 0.03)	0.16 (-0.41, 0.86)	0.32 (-0.35, 0.86)
Spouse BSI	-0.04 (-0.59, 0.45)	-0.08 (-0.43, 0.26)	-0.07 (-0.46, 0.37)	-0.10 (-0.51, 0.31)
Intervention	1.58 (-12.89, 19.95)	-0.82 (-5.35, 3.71)	2.28 (-7.86, 12.75)	0.88 (-7.48, 11.07)
Baseline	0.00 (-0.07, 0.07)	0.96 (0.74, 1.18)	0.00 (-0.06, 0.05)	0.00 (-0.06, 0.06)
Spouse				
Intercept	7.74 (-6.17, 20.22)	15.17 (8.63, 21.71)	6.06 (-4.04, 18.36)	7.40 (-1.34, 17.77)
Time	-0.14 (-1.65, 1.32)	-0.59 (-1.67, 0.49)	0.52 (-0.89, 2.01)	-0.23 (-1.75, 1.11)
Spouse A-DAS	0.72 (0.25, 1.29)	0.41 (0.16, 0.66)	0.80 (0.47, 1.16)	0.74 (0.45, 1.04)
Spouse BSI	-0.06 (-0.32, 0.16)	-0.16 (-0.34, 0.02)	-0.01 (-0.14, 0.1)	-0.02 (-0.14, 0.09)
Patient A-DAS	-0.20 (-0.39, 0.08)	-0.05 (-0.19, 0.08)	-0.11 (-0.32, 0.08)	-0.12 (-0.26, 0.08)
Patient BSI	0.12 (-0.13, 0.39)	0.13 (-0.06, 0.32)	0.17 (0.01, 0.32)	0.07 (-0.06, 0.23)
Intervention	-2.59 (-5.28, 0.39)	-1.81 (-4.19, 0.58)	-2.14 (-5.29, 1.34)	-2.58 (-5.62, 0.02)
Baseline	0.00 (-0.03, 0.03)	0.00 (-0.13, 0.13)	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)