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RESEARCH ARTICLE

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Bayesian sensitivity analyses for longitudinal data with dropouts that are potentially missing not at random: A high dimensional pattern-mixture model

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Abstract

Randomized clinical trials with outcome measured longitudinally are frequently analyzed using either random effect models or generalized estimating equations. Both approaches assume that the dropout mechanism is missing at random (MAR) or missing completely at random (MCAR). We propose a Bayesian pattern-mixture model to incorporate missingness mechanisms that might be missing not at random (MNAR), where the distribution of the outcome measure at the follow-up time t_k, conditional on the prior history, differs across the patterns of missing data. We then perform sensitivity analysis on estimates of the parameters of interest. The sensitivity parameters relate the distribution of the outcome of interest between subjects from a missing-data pattern at time t_k with that of the observed subjects at time t_k. The large number of the sensitivity parameters is reduced by treating them as random with a prior distribution having some pre-specified mean and variance, which are varied to explore the sensitivity of inferences. The missing at random (MAR) mechanism is a special case of the proposed model, allowing a sensitivity analysis of deviations from MAR. The proposed approach is applied to data from the Trial of Preventing Hypertension.

KEYWORDS

clinical trials, hypertension, missing data, MNAR future dependent, tipping point analysis, TROPHY trial

1 | INTRODUCTION

Missing data are a common problem in statistical modeling of longitudinal studies where subjects drop out prematurely before study completion. A wide range of statistical models for analyzing outcomes with missing data is available, with their performance depending on validity of their underlying assumptions. Approaches include pattern-mixture models (PMM),[1,2] selection models (SM),[3-5] and shared-parameter models[6,7]

In longitudinal studies, the dropout mechanism is missing not at random (MNAR) if the probability of dropping out at time t depends on y_t and/or $y_{t+1}, \ldots, y_K$. When the probability of dropping out at time t depends on future unobserved values $y_{t+1}, \ldots, y_K$, the dropout mechanism is future dependent MNAR.[8] When the number of follow-up visits increases, modeling missingness mechanism becomes high dimensional and challenging regardless of the approach used. To deal

Abbreviations: MAR, missing at random, MCAR, missing completely at random, MNAR, missing not at random, TROPHY, trial of preventing hypertension.

with high dimensionality, Roy and Daniels[9] use a latent class PMM, Zhang et al[10] use a factor-model imputation, Wang et al[11] use a Bayesian shrinkage model, Scharfstein et al[12] used a SM with a low-dimensional parameterization for the dropout mechanism.

The choice of approach is usually based on the analysis objectives, how best to formulate and incorporate assumptions about the missingness mechanism, the robustness of each model, the availability of programs to fit the model, and the flexibility and interpretability of the sensitivity analysis. The SM estimates the marginal parameter of interest directly, whereas PPM estimate separate parameters for each missing-data pattern, then derive marginal parameters by weighting across missing-data patterns,[13] or alternatively by applying PMM with multiple imputation.[14] For cross-sectional data there is a relationship between the SM and PMM approaches,[15] which can make the use of each model interchangeable. However, for longitudinal data an explicit connection between SM and PMM is often complicated, especially for future dependent MNAR with a large number of missing-data patterns. Developing methods in this setting is challenging and an active area of research. For recent work see Wang and Daniels[16] who use PMM; Scharfstein et al[12] who use SM, and Linero and Daniels[17] who use Bayesian models. Regardless of the model, assumptions that are non-verifiable from the observed data are needed to identify some of the parameters in the joint distribution, and assessing these assumptions requires a sensitivity analysis.[18,19] A National Research Council report on missing data in clinical trials[20] includes the following recommendation (# 15) in dealing with missing data in clinical trials: "*Sensitivity analysis should be part of the primary reporting of clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting*".

1.1 | TROPHY trial

Our work was motivated by the Trial Of Preventing Hypertension (TROPHY)[21,22] an investigator-initiated study to examine whether early treatment of prehypertension might prevent or delay the development of hypertension. TROPHY's primary objective was to determine whether for patients with prehypertension, two years of treatment with candesartan would reduce the systolic and diastolic blood pressure and subsequently the incidence of hypertension for up to two years after active treatment was discontinued. The study consisted first of a two-year double-blind, placebo-controlled phase; followed by a two-year phase in which all study patients received a placebo. Subjects were examined every three months, as well as one month after the beginning of each phase. The development of hypertension was chosen as the primary study event. After an event occurred, antihypertension treatment with metoprolol, hydrochlorothiazide, and some other medications was offered at no cost.

After the TROPHY trial and other studies, the American College of Cardiology and the American Heart Association (ACC/AHA) provided in 2017 a coherent and clinically relevant guideline[23] to health care providers for the prevention, detection, evaluation, and management of high blood pressure. Under the new guidelines, what was defined as prehypertension in TROPHY study (systolic blood pressure of 130-139 mm Hg and diastolic pressure of 89 mm Hg or lower, and systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg), is now considered Stage 1 hypertension. Important issues related to these new diagnostic thresholds, intensified treatment goals, and their implications for clinical practice are discussed by Byrd and Brooks.[24] Given the new guidelines, in this paper we focus on making inferences on the effect of candesartan during the active treatment period (baseline to 24 months) in controlling the diastolic blood pressure (DBP) from the high range of 85-90 of Stage 1 hypertension to the new recommended value of below 80, and the methodological challenges that are related to increasing missing or censored data. Specifically, DBP data are considered (1) missing if subjects dropped out before developing hypertension; and (2) censored when subjects developed hypertension and following the protocol other more aggressive pharmacological treatment of blood pressure was initiated; in that case the follow-up DBP data are affected and cannot be used for estimating the candesartan effect. The counterfactual question is: what would the values of blood pressure be in each treatment group if we had not intervened with other drugs after development of hypertension? In addition, some subjects occasionally missed scheduled visits and had intermittent missing data; we consider them to be missing at random (MAR).

1.2 | Modeling missing data

We propose new models to address the problem related to missing data in TROPHY study; such models, however, can be used for analyses of other similar longitudinal studies with dropouts. A range of models for imputing

missing values is available. For example, missing values are imputation using a MAR model and then to allow for MNAR a δ value (ie, δ-adjustment) is added, which captures the mean difference δ between MNAR and MAR models.[25] Rather than modeling the mean, Wang and Feng[26] and Tang et al[27] use quantile based imputation for imputing missing values. However, in longitudinal studies the dropouts can differ from observed subjects not only with respect to means or quantiles, but also with respect to within-subject autocorrelations. Specific to the TROPHY study, well known risks on cardiovascular events are high blood pressure and the visit-to-visit variability (VVV) in blood pressure, where higher VVV is associated with higher risk of cardiovascular events or deaths.[28] The visit-to-visit variability is effected by the variance at each visit and the strength of the visit-to-visit association.[29] Thus, if the dropout mechanism depends on the risk of cardiovascular events we propose a sensitivity analysis that simultaneously captures differences in mean, variance, and visit-to-visit associations, by varying parameters summarizing each of these features.

In randomized clinical trials, the target population is often an at-risk or affected population, where the distribution $f(y_1)$ of the primary outcome Y_1 at baseline is restricted. In the TROPHY study, the distribution for Y_1 is truncated and not normal, requiring methods that are robust to any distributional assumption about $f(y_1)$ or the multivariate distribution of Y.

We propose here a Bayesian pattern-mixture model for MNAR data that is flexible for modeling future dependent missingness, is distribution-free for $f(y_1)$, and can accommodate a large number of measurements over time. We introduce sensitivity parameters that capture differences in means, variances, and visit-to-visit associations between dropouts and observed subjects. We develop and implement a Bayesian algorithm in JAGS (Just Another Gibbs Sampler: https://sourceforge.net/projects/mcmc-jags) for fitting the model and performing sensitivity analyses.

The number of unidentified parameters in the proposed model is substantial, and increases rapidly at the order of $O(K^3)$, where K is the number of the dropout patterns. To deal with this problem, we use a Bayesian approach similar to Kaciroti et al,[30] where the number of sensitivity parameters is reduced by considering them to be randomly chosen from a prior distribution. This prior distribution links all these parameters together around an average missingness mechanism (mean parameter), while accommodating possible differences among them by introducing random variation (variance parameter); the mean and variance then become the parameters for sensitivity analysis. The sensitivity parameters are easy to understand; they relate the distribution of the observed data at time t to that of the missing data at time t across different missing-data patterns. The parameterization and the associated prior distribution provide for modeling different types of MAR and MNAR missing data. The model also enables a sensitivity analysis for MNAR departures from MAR.[31]

In Section 2 we outline the general model when the missingness mechanism is MAR and expand this in Section 3 to missing data that are MNAR. In Section 4 we describe the Bayesian approach used to fit the proposed model. In Section 5 we apply the proposed model to TROPHY data. Section 6 provide results of simulation studies. Conclusions are given in Section 7.

2 | BAYESIAN MODEL UNDER MAR

Let $Y = (Y_1, Y_2, \ldots, Y_K)'$ be a vector of K repeated measures, where Y_1 denotes the baseline (pre-randomization) value measured at time $t_1 = 0$, and Y_k denotes the outcome at visit k measured at follow-up time t_k, $k = 2, \ldots, K$. Let R denote the dropout pattern, where $R = r$ indicates the last visit (r) a subject was observed, with $R = K$ being the complete data pattern. Let Z be a treatment indicator $Z = z$ for $z = 0, 1$. We are interested in estimating the expected mean for a subject i in group z at each visit k:

$$E(Y_{ik}|Z = z) = \mu_{zk},$$

and testing for group differences in the outcome Y during the whole study period from $k = 1$ to K. In presence of dropouts, we propose a Bayesian pattern-mixture model that incorporates different assumptions about the missingness mechanism into the final analysis. These assumptions are based on quantifying the differences between dropout subjects and observed subjects, and allow sensitivity analysis using the MAR assumption as a reference. We assume that the mean for subjects in group z at visit $k \geq 2$ from pattern $R = r$, depends on previous responses $\underline{Y}_{zk-1} = (Y_{z1}, \ldots Y_{zk-1})$ and relevant baseline covariates $X = (X_1, X_2, \ldots, X_p)$. Controlling for covariates X, makes the MAR assumption more likely, improves the

normality of the residuals and reduces their variance, consequently resulting in a better imputation model. We assume the following distribution for pattern $R = r$:

$$f(Y_{zk}|X, \underline{Y}_{zk-1}, R = r) = N(\mu^{(r)}_{zk|k^-}, \sigma^{2^{(r)}}_{zk|k^-}), \tag{1}$$

where $E(Y_{zk}|X, \underline{Y}_{zk-1}, R = r) = \mu^{(r)}_{zk|k^-}$ and $Var(Y_{zk}|X, \underline{Y}_{zk-1}, R = r) = \sigma^{2^{(r)}}_{zk|k^-}$ are the conditional mean and the conditional variance among subjects in group z, pattern $R = r$, for $k \geq 2$.

The means and variances in (1) are not all identified as there are no data to estimate $\mu^{(r)}_{izk|k^-}$ and $\sigma^{2(r)}_{zk|k^-}$ for $k \geq 2, r < k$. To identify the model, we relate the distribution of the missing data at visit k to that of the observed data at visit k conditioned on baseline covariates and the previous responses. Following the available-case missing value (ACMV) constraint,[32] the missingness mechanism is MAR if and only if for $\forall\, k \geq 2$, $r < k$, and $\forall\, z$ the following is true:

$$f(Y_{zk}|X, \underline{Y}_{zk-1}, R = r) = f(Y_{zk}|X, \underline{Y}_{zk-1}, R \geq k), \tag{2}$$

here $(R \geq k)$ corresponds to the observed data at visit k. We assume the following distribution of the observed data at visit $k \geq 2$ for $R \geq k$

$$f(Y_{zk}|X, \underline{Y}_{zk-1}, R \geq k) = N(\mu^{(\geq k)}_{zk|k^-}, \sigma^{2^{(\geq k)}}_{k|k^-}). \tag{3}$$

Here $\mu^{(\geq k)}_{zk|k^-}$ and $\sigma^{2^{(\geq r)}}_{zk|k^-}$ are the mean and the variance of the observed data for Y_{zk}, conditioned on X and $\underline{Y}_{zk-1}$ among subjects in patterns $R \geq k \geq 2$. The conditional mean $\mu^{(\geq k)}_{zk|k^-}$ can be any parametric function of X and previous responses; here it is assumed to be linear:

$$\mu^{(\geq k)}_{zk|k^-} = \beta^{(\geq k)}_{0zk} + \sum_{l=1}^{k-1} \beta^{(\geq k)}_{lzk}(y_{zk-l} - \overline{y}^{(\geq k)}_{zk-l}) + \alpha^{(\geq k)}_{zk}(x - \overline{x})^T,$$

where the intercept $\beta^{(\geq k)}_{0zk}$ represents the expected value of $Y^{(\geq k)}_{zk|k^-}$ for an average subject with previous BP and covariates values equal to $\overline{y}^{(\geq k)}_{z1}, \overline{y}^{(\geq k)}_{z2}, \ldots, \overline{y}^{(\geq k)}_{zk-1}$ and $\overline{x}$. $\beta^{(\geq k)}_{lzk}$ is the lth order autoregression coefficient, and $\alpha^{(\geq k)}_{zk} = (\alpha^{(\geq k)}_{1zk}, \ldots, \alpha^{(\geq k)}_{pzk})$ are the regression parameters for $X = (X_1, \ldots, X_p)$.

From (1), (2), and (3) the missingness mechanism is MAR if and only if $\mu^{(r)}_{zk|k^-} = \mu^{(\geq k)}_{zk|k^-}$ and $\sigma^{2^{(r)}}_{zk|k^-} = \sigma^{2^{(\geq r)}}_{zk|k^-}$ for $k \geq 2$, $r < k$, and $\forall z$. Consequently, under a MAR assumption following Molenberghs et al[32] we have:

$$f(Y_{zk}|X, \underline{Y}_{zk-1}) = N(\mu^{(\geq k)}_{zk|k^-}, \sigma^{2(\geq k)}_{zk|k^-}),$$

and $\mu^{(\geq k)}_{zk|k^-} = \beta^{(\geq k)}_{0zk} + \sum_{l=1}^{k-1} \beta^{(\geq k)}_{lzk}(y_{zk-l} - \overline{y}^{(\geq k)}_{zk-l}) + \alpha^{(\geq k)}_{zk}(x - \overline{x})^T$ for $k = 2, 3, \ldots, K$. Note that there is no assumption about the distribution of baseline measure Y_1 or on the multivariate distribution of Y.

Some subjects occasionally missed scheduled visits and had intermittent missing data. Let I_{ik} be the intermittent missing indicator, which is equal to 1 if subject i has an intermittent missing value at visit k and 0 otherwise when $R_{ik} \geq k$ (ie, subjects i has not dropped out by visit k). We assume that any intermittent missing value is MAR within the observed pattern $(R_{ik} \geq k)$, or:

$$f(Y_{izk}|\underline{Y}_{izk-1}, R_{ik} \geq k, I_{ik} = 1) = f(Y_{ik}|\underline{Y}_{ik-1}, R_{ik} \geq k, I_{ik} = 0).$$

The implementation under the Bayesian approach is straight forward, where the subject i with missing intermittent value at visit k is imputed using a draw from $f(Y_{ik}|\underline{Y}_{ik-1}, R_{ik} \geq k)$ (the observed data model), and values after dropout or censoring imputed treating the imputed intermittent values like observed values.

3 | EXPANDED MODEL FOR MNAR MECHANISMS

Under a MNAR missingness mechanism we assume a sequential pattern-mixture model with normal distributions (2) for the observed data and (3) for the missing data. The models are unidentified as there are no data to estimate $\mu^{(r)}_{zk|k^-}$

and $\sigma^{2(r)}_{zk|k^-}$ for $k \geq 2$, $r < k$, and $z = 0, 1$. For monotone missing data, the ACMV restriction is equivalent to MAR. Here we extend the ACMV approach to identify the PMM when missing data are MNAR, and provide for a sensitivity analysis around MAR. For MNAR the identifying constraints relate the distribution of the missing data to that of the observed data. Because there are no data to estimate the identifying constraints, it is useful to have intuitive and easy-to-interpret parameters, which can then be evaluated using a sensitivity analysis. We propose identifying constraints for the parameters of the missing-data patterns by relating them to the parameters of the observed data as follows:

$$\mu^{(r)}_{zk|k^-} = \beta^{(r)}_{0zk} + \sum_{l=1}^{k-1} \beta^{(r)}_{lzk}(y_{zk-l} - \bar{y}^{(\geq k)}_{zk-l}) + \alpha^{(r)}_{zk}(x - \bar{x})^T, \tag{4}$$

where

$$\beta^{(r)}_{0zk} = \beta^{(\geq k)}_{0zk} + \tilde{\lambda}^{(r)}_{zk}$$

$$\beta^{(r)}_{lzk} = \beta^{(\geq k)}_{lzk}(1 + \tilde{\delta}^{(r)}_{lzk})$$

$$\sigma^{2^{(r)}}_{zk|k^-} = \tilde{\psi}^{(r)}_{zk}\sigma^{2^{(\geq k)}}_{zk|k^-}$$

$\forall\, k \geq 2$, $r < k$, and $z = 0, 1$. We assume here that $\alpha^{(r)}_{zk} = \alpha^{(\geq k)}_{zk} = \alpha_{zk}$, but similar constraints to the one used for $\beta^{(r)}_{lzk}$ can be introduced as needed.

Here $\tilde{\lambda}^{(r)}_{zk}$, $\tilde{\delta}^{(r)}_{lzk}$, and $\tilde{\psi}^{(r)}_{zk}$ are the sensitivity parameters used to identify the model. The $\tilde{\lambda}^{(r)}_{zk}$ measures the difference between location parameters $\mu^{(r)}_{zk|k^-}$ and $\mu^{(\geq k)}_{zk|k^-}$ at visit k for group z. That is, $\tilde{\lambda}^{(r)}_{zk}$ is the expected difference at visit k between an "*average*" subject in observed pattern ($\geq k$) and a similar subject from a missing pattern r for group z. "*Average*" is defined as a subject whose previous BP and covariates values are equal to $\bar{y}^{(\geq k)}_{z1}, \bar{y}^{(\geq k)}_{z2}, \ldots, \bar{y}^{(\geq k)}_{zk-1}$ and $\bar{x}_z$; $\tilde{\delta}^{(r)}_{lzk}$ represents the relative difference in lag-l associations between subjects in missing pattern r at visit k with subjects from the observed data at visit k for group z; and $\tilde{\psi}^{(r)}_{zk}$ represents the ratio of residual variances for the missing data in pattern r at visit k with the observed data at visit k, for group z condition on the previous measures.

The proposed PMM is a high dimensional when the number of follow-up measures is large. To reduce the number of sensitivity parameters one could fix them to a common value, that is, $\tilde{\lambda}^{(r)}_{zk} = l_z$, $\tilde{\delta}^{(r)}_{lzk} = d_z$, and $\tilde{\psi}^{(r)}_{zk} = a_z$. We propose here a more general approach, by assuming them to have a common mean, but allowing for uncertainty around the mean as follows:

$$\tilde{\lambda}^{(r)}_{zk} \sim N(l_z, c^2 l_z^2)$$
$$\tilde{\delta}^{(r)}_{lzk} \sim N(d_z, c^2 d_z^2)$$
$$\tilde{\psi}^{(r)}_{zk} \sim Log - Normal(a_z, c^2 a_z^2)$$

The sensitivity parameters are now reduced to $\omega = (c, l_0, l_1, d_0, d_1, a_0, a_1)$, where $a_z > 0$ and c is the coefficient of variation. With this approach we can quantify the differences between the missing subjects vs. observed subjects by providing an average value $\pm$ some range, with the deterministic constrain being a special case when $c = 0$.

4 | FITTING THE MODEL

The parameters of interest are the marginal growth curves $\mu_z = (\mu_{z1}, \mu_{z2}, \ldots, \mu_{zK})'$ for each group z as if no subject was missing or treated with other medications after they developed hypertension. We use a fully Bayesian approach to impute draws of the missing data, then derive inference on the marginal parameters using Bayesian bootstrapping[33] on the whole (observed and drawn) data. The missing data are drawn based on the joint posterior distribution $[\tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, \alpha, \beta, \Sigma, Y^{(Miss)}|Data, l, d, a, c]$. Here, $Data = (z, x, y_1, y_2^{(\geq 2)}, y_3^{(\geq 3)}, \ldots, y_K^{(\geq K)})$; $\alpha = \{(\alpha_{1zk}, \alpha_{2zk} \ldots \alpha_{pzk})|k = 2, \ldots, K, z \in Z\}$ and $\beta = \{\beta^{(\geq k)}_{lzk}, |l = 0, \ldots, k-1, k = 2, \ldots, K, z \in Z\}$ are the set of α and β parameters for the observed data; $\Sigma = \{\sigma^{2(\geq k)}_{zk|k^-}|k = 2, \ldots, K, z \in Z\}$ is the set of $\sigma^{2(\geq k)}_{zk|k^-}$ parameters for the observed data; $Y^{(Miss)} = (y_2^{(1)}, y_3^{(1)}, y_3^{(2)}, \ldots, y_K^{(1)}, \ldots, y_K^{(K-1)})$ are the missing data; $\tilde{\lambda} = \{\tilde{\lambda}^{(r)}_{zk}|k \geq 2, r = 1, \ldots, k-1, z \in Z\}$; $\tilde{\delta} = \{\tilde{\delta}^{(r)}_{lzk}|k \geq$

$2, l = 1, \ldots, k-1, r = 1, \ldots, k-1, z \in Z\}$; and $\tilde{\psi} = \{\tilde{\psi}_{zk}^{(r)} | k \geq 2, r = 1, \ldots, k-1, z \in Z\}$. The joint posterior distribution can be decomposed as a product of three distributions:

$$[\tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, \alpha, \beta, \Sigma, Y^{(Miss)} | Data, l, d, a, c] = \underbrace{[\tilde{\lambda}, \tilde{\delta}, \tilde{\psi} | Data, l, d, a, c]}_{1}$$
$$\underbrace{[\alpha, \beta, \Sigma | \tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, Data, l, d, a, c]}_{2}$$
$$\underbrace{[Y^{(Miss)} | \tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, \alpha, \beta, \Sigma, Data, l, d, a, c]}_{3}$$

Then, imputations from the joint distribution are drawn sequentially from distribution 1, 2, and 3 as follows.

4.1 | Draw from $[\tilde{\lambda}, \tilde{\delta}, \tilde{\psi} | Data, l, d, a, c]$

In a PMM setting the data provide no evidence for sensitivity parameters,[13] or:

$$[\tilde{\lambda}, \tilde{\delta}, \tilde{\psi} | Data, l, d, a, c] = [\tilde{\lambda} | l, c][\tilde{\delta} | d, c][\tilde{\psi} | a, c].$$

Thus, $\tilde{\lambda}_{zk}^{(r)}, \tilde{\delta}_{zk}^{(r)}, \tilde{\psi}_{zk}^{(r)}$ for group z are drawn from

$$\tilde{\lambda}_{zk}^{(r)} \sim \mathcal{N}(l_z, c^2 l_z^2)$$
$$\tilde{\delta}_{lzk}^{(r)} \sim \mathcal{N}(d_z, c^2 d_z^2)$$
$$\tilde{\psi}_{zk}^{(r)} \sim Log - Normal(a_z, c^2 a_z^2).$$

4.2 | Draw from $[\alpha, \beta, \Sigma | \tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, Data, l, d, a, c]$

Within the PMM the fit of the model to the observed data is identical for all choices of sensitivity parameters and does not depend on the missing data,[13] that is:

$$[\alpha, \beta, \Sigma | \tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, Y^{(Miss)}, Data, l, d, a, c] = [\alpha, \beta, \Sigma | Data].$$

Here,

$$[\alpha, \beta, \Sigma | Data] = \prod_{k=2}^{K} f(y_k^{(\geq k)} | z, x, y_1^{(\geq k)}, \ldots, y_{k-1}^{(\geq k)}, \alpha, \beta, \Sigma) f(y_1^{(\geq 1)} | x, z)[\alpha, \beta][\Sigma],$$

where

$$f(y_k^{(\geq k)} | z, x, y_1^{(\geq k)}, \ldots, y_{k-1}^{(\geq k)}, \alpha, \beta, \Sigma) = N(\mu_{zk|k^-}^{(\geq k)}, \sigma_{zk|k^-}^{2(\geq k)}).$$

Thus the observed data model is fitted based on a set of linear regression models where $\mu_{zk|k^-}^{(\geq k)} = \beta_{0zk}^{(\geq k)} + \sum_{l=1}^{k-1} \beta_{lzk}^{(\geq k)} (y_{k-l} - \overline{y}_{k-l}^{(\geq k)}) + \alpha_{zk}(x - \overline{x})$ for $k = 2, 3, \ldots, K$ with noninformative prior distributions for α, β, and Σ.

4.3 | Draw from $[Y^{(Miss)} | \tilde{\lambda}, \tilde{\delta}, \tilde{\psi}, \alpha, \beta, \Sigma, Data, l, d, a, c]$

This is the imputation step, where the missing values are drawn from their posterior distribution. Let $y_k^{(r)}$ be missing value at visit k for a subject from group z in missing pattern r, $k = 2, \ldots, K$ and $2 \leq r < k$. Then,

$$f(y_k^{(r)} | z, x, y_{-k-1}, \alpha, \beta, \Sigma, \tilde{\lambda}, \tilde{\delta}, \tilde{\psi}) = N(\mu_{zk|k^-}^{(r)}, \sigma_{zk|k^-}^{2(r)}),$$

where following (4):

$$\mu^{(r)}_{z k|k^-} = (\beta^{(\geq r)}_{0zk} + \tilde{\lambda}^{(r)}_{zk}) + \sum_{l=1}^{k-1} \beta^{(\geq r)}_{lzk}(1 + \tilde{\delta}^{(r)}_{lzk})(y_{k-l} - \bar{y}^{(\geq k)}_{k-l}) + \alpha_{zk}(x - \bar{x})$$

and

$$\sigma^{2(r)}_{zk|k^-} = \tilde{\psi}^{(r)}_{zk} \sigma^{2(\geq k)}_{zk|k^-}.$$

Within this step, the draws of $y^{(r)} = (y^{(r)}_{r+1}, \ldots, y^{(r)}_K)$ are sequential: specifically, $y^{(r)}_{r+1}$ is drawn first, and next $y^{(r)}_{r+2}$ up to $y^{(r)}_k$, conditioned on the previous draws and the observed data.

In addition, any subject with an intermittent missing value, which is assumed MAR, is included in the observed data model and the intermittent missing value is automatically imputed as a drawn based on the observed data model.

4.4 | Draws of marginal parameters $\mu_z = (\mu_{z0}, \mu_{z1}, \ldots, \mu_{zK})'$

The parameter of interest are the marginal parameters $\mu_z = (\mu_{z0}, \mu_{z1}, \ldots, \mu_{zK})'$, where $E(Y_{zk}|Z = z) = \mu_{zk}$ for each treatment group z. Once the missing data are drawn, we can simulate draws of μ_z from the completed data (observed and drawn/imputed). This can be viewed as a multiple imputation and has been proposed in Demirtas and Schafer.[34] The likelihood function for μ_z is a mixture of distributions accross all missing patterns and a direct draw for μ_z is not feasible. We use Bayesian bootstrapping to draw inference on μ_z based on the full data set. The Bayesian bootstrapping reweights the completed data $Y = (Y_1, Y_2, \ldots, Y_K)'$ into a new bootstrap data set $\mathcal{D}$. Each observation $y_i \in \mathcal{D}, i = 1, 2, \ldots, N$ is weighted by $w_i = u_{(i+1)} - u_{(i)}$, where $u_{(i)}$ is the ith ordered statistics for $u_i \sim U[0, 1]$, $i = 2, \ldots, N$ and $u_{(1)} = 0$, $u_{(N+1)} = 1$. The distribution of $\mu_z = (\mu_{z0}, \mu_{z1}, \ldots, \mu_{zK})'$ from many such data sets $\mathcal{D}$ is then a simulation approximation of the posterior distributions on μ_z.[33]

4.5 | Sensitivity analysis

We vary l_z, d_z, a_z, and c in a sensitivity analysis. For example, when the missing data are MAR, then all $\tilde{\lambda}^{(r)}_{zk} = \tilde{\delta}^{(r)}_{lzk} = 0$, and $\tilde{\psi}^{(r)}_{zk} = 1$, or $l_z = d_z = c = 0$ and $a_z = 1$. Alternatively, when the missing data are MNAR, then not all $\tilde{\lambda}^{(r)}_{zk}$'s, $\tilde{\delta}^{(r)}_{lzk}$'s equal to 0 and $\tilde{\psi}^{(r)}_{zk}$'s equal to 1. Thus l_z, d_z, and a_z can measure deviations from MAR. Trying values of sensitivity parameters in a neighborhood of the MAR ($l_z, d_z \approx 0$, $a_z \approx 1$, and small c), can often provide reassuring information about whether the inferences are robust to moderately non-ignorable missingness mechanisms. Tipping point sensitivity analyses to find values l_z, d_z, a_z, and c, for which group comparisons are borderline significant (ie, *P-value*=.05), are also useful, to assess how far from MAR the missingness mechanism must be for treatment differences to lose the statistical significance.[35,36]

4.6 | Implementation using JAGS

We used *run.jags* and *rjags* packages in RStudio to fit the model. The following noninformative prior distributions were used for the parameters of the observed data model: α_{pzk}, $\beta^{(\geq k)}_{lzk} \sim N(0, 10000)$, and $\sigma^{(\geq k)}_{zk|k^-} \sim U(0, 20)$. We run 1000 iterations for adapting phase with another 4000 burn in iterations. The final inferences were based on 10 000 additional iterations. Two chains, each using different initial values, were used to calculate the Deviance Information Criteria (DIC) using *run.jags*. The 3^{rd}-order autoregression model $A(3)$ was used for imputation as higher order autoregression models increased the DIC. The MCMC simulations had good mixing with lag-10 autocorrelations all around zero. The MCMC convergence was monitored using the Gelman-Rubin convergence diagnostic,[37] where all potential scale reduction factor were around 1. The ratios of Monte Carlo standard errors of each parameter to the posterior standard deviations were very small $MCSE/SD < 1\%$, indicating that the Markov chain has stabilized and the mean estimates do not vary much over time. Because the Markov chain for our model converged without difficulty, we used one single chain for running simulation studies to reduce the computational time.

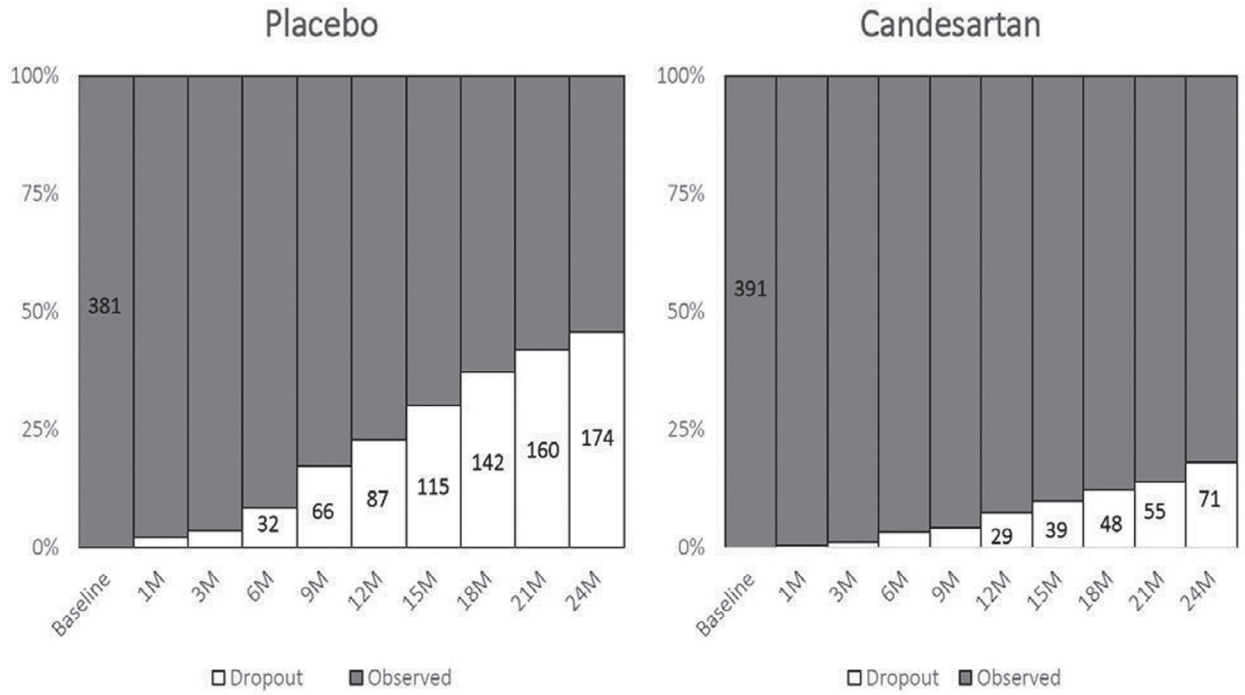


FIGURE 1 Missing data pattern for each group

5 | APPLICATION

5.1 | The TROPHY data

In this section we apply the method described in Section 3 to the data from the TROPHY study. The study population consisted of 772 patients randomly assigned to candesartan (391) or placebo (381). Among the 772 participants 109 (54 in placebo) dropped out before developing hypertension. Also, 136 (120 in placebo) subjects developed hypertension and their DBP were censored, after other BP medications were initiated. Thus, 245 subjects had a missing or censored DBP (174 in the placebo group). Sometimes a subject missed a schedule visit but came back later. The fraction of intermittent missing values was very low, and such missingness were expect to be unrelated to BP and hence MAR—that is, a subject missed a visit due to schedule conflicts or other reasons not related to BP, but came back for future visits. Figure 1 shows the rates of missing data, which are higher for subjects in the placebo group.

The effect of candesartan—compared to placebo—in reducing DBP is estimated both over the 24 months period, as well as at 24 months.

5.2 | Sensitivity analysis

Sensitivity analyses to assess the deviations from MAR ($l_z = 0$, $d_z = 0$, $a_z = 1$, $c = 0$) are performed to assess the effect of the missing data on the final results. We consider $d_z = 0, 0.3, -0.3$ and $a_z = 1, 1.3, 0.7$, which reflect no difference, 30% increase, or 30% decrease in the lag-associations and residual variance respectively, between subjects from a missing pattern versus subjects from the observed data pattern. We vary l_z at -2, 2, and 0, which reflect a medium Cohen's effect size of $-0.5SD$ and $0.5SD$ (baseline $SD = 4.06$), or no difference between subjects from a missing pattern versus subjects from the observed data pattern. A value of $l_z > 0$ indicates that, on average, subjects in a missing pattern have higher DBP than the observed subjects—and the opposite would be true for $l_z < 1$. We set $c = .3$, which provides a range for $\tilde{\lambda}_{zk}^{(r)}$ with a 95%CI of $l_z^{(r)}(1 \pm .59)$.

In addition, sensitivity analyses based on assumptions that make the treatment effect borderline significant, $l_z = \bar{l}_z$, $d_z = \bar{d}_z$, and $a_z = \bar{a}_z$ are also included. We focus on $\bar{l}_z$ as the tipping-point parameter, because it has the highest impact

TABLE 1 Sensitivity analysis under alternative dropout mechanisms with $d_0 = d_1 = 0$

Sensitivity parameters (c=0.3)	Placebo	Candesartan	Difference (Δ)
$l_0 = l_1 = 0$			
$a_0 = a_1 = 1$ (MAR)	84.3 (.54)	78.6 (.42)	−5.7 (−7.1,−4.4)
$a_0 = a_1 = 1.3$	84.3 (.56)	78.6 (.43)	−5.7 (−7.1,−4.3)
$a_0 = a_1 = 0.7$	84.3 (.51)	78.6 (.39)	−5.7 (−7.0,−4.5)
$l_0 = 0, l_1 = 2$			
$a_0 = a_1 = 1$	84.3 (.54)	79.3 (.44)	−5.0 (−6.4,−3.7)
$a_0 = a_1 = 1.3$	84 .3 (.56)	79.3 (.45)	−5.0 (−6.5,−3.6)
$a_0 = a_1 = 0.7$	84.3 (.51)	79.3 (.43)	−5.0 (−6.4,−3.7)
$l_0 = -2, l_1 = 0$			
$a_0 = a_1 = 1$	82.5 (.51)	78.6 (.42)	−3.9 (−5.2,−2.7)
$a_0 = a_1 = 1.3$	82.5 (.54)	78.6 (.44)	−3.9 (−5.3,−2.6)
$a_0 = a_1 = 0.7$	82.5 (.47)	78.6 (.40)	−3.9 (−5.1,−2.7)
$l_0 = -2, l_1 = 2$			
$a_0 = a_1 = 1$	82.5 (.52)	79.3 (.44)	−3.2 (−4.5,−1.9)
$a_0 = a_1 = 1.3$	82.5 (.53)	79.3 (.46)	−3.2 (−4.5,−1.9)
$a_0 = a_1 = 0.7$	82.5 (.47)	79.3 (.43)	−3.2 (−4.4,−1.9)
$l_0 = -2, l_1 = -2$			
$a_0 = a_1 = 1$	82.5 (.51)	77.9 (.41)	−4.6 (−5.9,−3.3)
$a_0 = a_1 = 1.3$	82.5 (.54)	77.9 (.43)	−4.6 (−6.0,−3.2)
$a_0 = a_1 = 0.7$	82.5 (.48)	77.9 (.40)	−4.6 (−5.8,−3.4)
$l_0 = 2, l_1 = -2$			
$a_0 = a_1 = 1$	86.1 (.62)	77.9 (.41)	−8.2 (−9.7,−6.8)
$a_0 = a_1 = 1.3$	86.1 (.64)	77.9 (.43)	−8.2 (−9.7,−6.7)
$a_0 = a_1 = 0.7$	86.1 (.60)	77.9 (.39)	−8.2 (−9.7,−6.9)
$l_0 = 2, l_1 = 2$			
$a_0 = a_1 = 1$	86.1 (.62)	79.3 (.44)	−6.9 (−8.4,−5.4)
$a_0 = a_1 = 1.3$	86.1 (.64)	79.3 (.46)	−6.8 (−8.4,−5.3)
$a_0 = a_1 = 0.7$	86.1 (.59)	79.3 (.43)	−6.8 (−8.3,−5.4)
$\bar{l}_0 = -4.7, \bar{l}_1 = 0$			
$\bar{a}_0 = \bar{a}_1 = 1$	80.1 (.60)	78.6 (.42)	−1.5 (−2.9,0.0)[a]
$a_0 = a_1 = 1.3$	80.1 (.61)	78.6 (.43)	−1.5 (−2.9,0.0)
$a_0 = a_1 = 0.7$	80.1 (.57)	78.6 (.40)	−1.5 (−2.9,−0.1)
$\bar{l}_0 = 0, \bar{l}_1 = 11.5$			
$\bar{a}_0 = \bar{a}_1 = 1$	84.3 (.53)	82.5 (.73)	−1.8 (−3.7,0.0)[a]
$a_0 = a_1 = 1.3$	84.3 (.56)	82.5 (.77)	−1.8 (−3.7,0.0)
$a_0 = a_1 = 0.7$	84.3 (.51)	82.5 (.74)	−1.8 (−3.6,0.1)
$\bar{l}_0 = -3.46, \bar{l}_1 = 3.46$			
$\bar{a}_0 = \bar{a}_1 = 1$	81.2 (.54)	79.8 (.48)	−1.4 (−2.8,0.0)[a]
$a_0 = a_1 = 1.3$	81.2 (.56)	79.8 (.49)	−1.4 (−2.9,0.1)
$a_0 = a_1 = 0.7$	81.2 (.51)	79.8 (.46)	−1.4 (−2.8,0.0)

[a]Bordeline significant: *P*-value = .05.

TABLE 2 Sensitivity analysis under alternative dropout mechanisms with $d_0 = d_1 = 0.3$

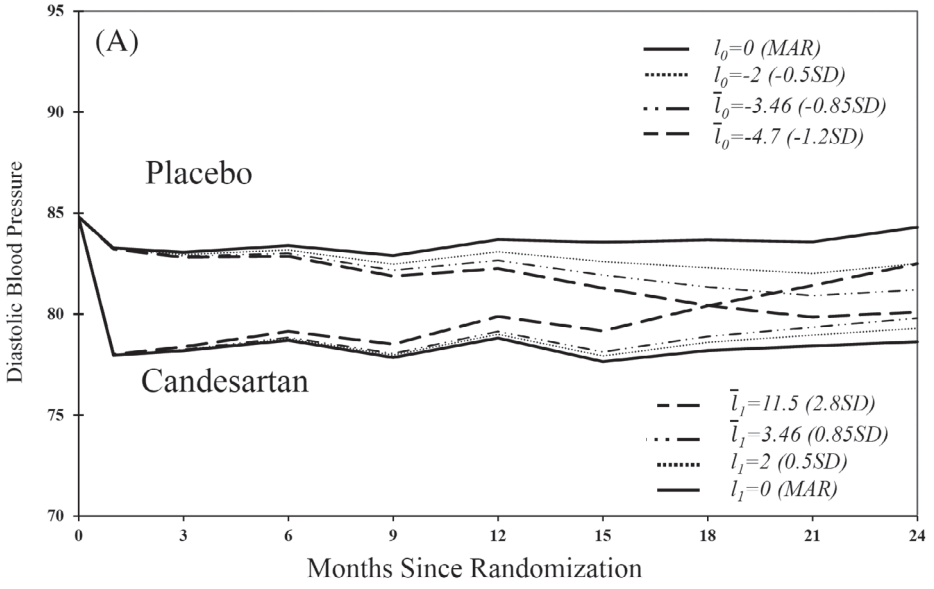
Sensitivity parameters (c=0.3)	Placebo	Candesartan	Difference (Δ)
$l_0 = l_1 = 0$			
$a_0 = a_1 = 1$ (MAR)	85.5 (.69)	79.1 (.47)	−6.4 (−8.1,−4.8)
$a_0 = a_1 = 1.3$	85.5 (.72)	79.1 (.49)	−6.4 (−8.2,−4.8)
$a_0 = a_1 = 0.7$	85.5 (.66)	79.1 (.45)	−6.4 (−8.1,−4.9)
$l_0 = 0, l_1 = 2$			
$a_0 = a_1 = 1$	85.5 (.70)	79.9 (.52)	−5.6 (−7.3,−3.9)
$a_0 = a_1 = 1.3$	85.5 (.71)	79.9 (.54)	−5.6 (−7.4,−3.8)
$a_0 = a_1 = 0.7$	85.5 (.68)	79.9 (.50)	−5.6 (−7.2,−3.9)
$l_0 = -2, l_1 = 0$			
$a_0 = a_1 = 1$	83.2 (.63)	79.1 (.47)	−4.1 (−5.6,−2.6)
$a_0 = a_1 = 1.3$	83.2 (.65)	79.1 (.49)	−4.1 (−5.7,−2.5)
$a_0 = a_1 = 0.7$	83.2 (.59)	79.1 (.45)	−4.1 (−5.5,−2.7)
$l_0 = -2, l_1 = 2$			
$a_0 = a_1 = 1$	83.2 (.62)	79.9 (.52)	−3.2 (−4.8,−1.6)
$a_0 = a_1 = 1.3$	83.2 (.65)	79.9 (.53)	−3.2 (−4.9,−1.6)
$a_0 = a_1 = 0.7$	83.2 (.59)	79.9 (.51)	−3.2 (−4.7,−1.7)
$l_0 = -2, l_1 = -2$			
$a_0 = a_1 = 1$	83.2 (.62)	78.2 (.45)	−5.0 (−6.5,−3.5)
$a_0 = a_1 = 1.3$	83.2 (.65)	78.2 (.47)	−5.0 (−6.6,−3.4)
$a_0 = a_1 = 0.7$	83.2 (.59)	78. (.43)	−5.0 (−6.4,−3.6)
$l_0 = 2, l_1 = -2$			
$a_0 = a_1 = 1$	87.9 (.86)	78.2 (.45)	−9.7 (−11.7,−7.8)
$a_0 = a_1 = 1.3$	87.9 (.89)	78.2 (.47)	−9.7 (−11.7,−7.7)
$a_0 = a_1 = 0.7$	87.9 (.84)	78.2 (.43)	−9.7 (−11.5,−7.9)
$l_0 = 2, l_1 = 2$			
$a_0 = a_1 = 1$	87.9 (.86)	79.9 (.52)	−7.9 (−9.9,−6.0)
$a_0 = a_1 = 1.3$	87.9 (.88)	80.0 (.54)	−7.9 (−10,−5.9)
$a_0 = a_1 = 0.7$	87.9 (.83)	79.9 (.51)	−7.9 (−9.8,−6.0)
$\bar{l}_0 = -4.1, \bar{l}_1 = 0$			
$\bar{a}_0 = \bar{a}_1 = 1$	80.7 (.68)	79.1 (.47)	−1.6 (−3.3,0.0)[a]
$a_0 = a_1 = 1.3$	80.7 (.70)	79.1 (.49)	−1.6 (−3.3,0.1)
$a_0 = a_1 = 0.7$	80.7 (.65)	79.1 (.45)	−1.6 (−3.2,−0.1)
$\bar{l}_0 = 0, \bar{l}_1 = 9.5$			
$\bar{a}_0 = \bar{a}_1 = 1$	85.5 (.69)	83.2 (.87)	−2.2 (−4.4,0.0)[a]
$a_0 = a_1 = 1.3$	85.5 (.73)	83.2 (.88)	−2.2 (−4.4,0.1)
$a_0 = a_1 = 0.7$	85.5 (.66)	83.2 (.86)	−2.2 (−4.3,−0.1)
$\bar{l}_0 = -3, \bar{l}_1 = 3$			
$\bar{a}_0 = \bar{a}_1 = 1$	82.0 (.63)	80.4 (.56)	−1.6 (−3.3,0.0)[a]
$a_0 = a_1 = 1.3$	82.0 (.66)	80.4 (.57)	−1.6 (−3.4,0.1)
$a_0 = a_1 = 0.7$	82.0 (.60)	80.4 (.55)	−1.6 (−3.2,0.0)

[a]Bordeline significant: *P*-value = .05.

TABLE 3 Sensitivity analysis under alternative dropout mechanisms with $d_0 = d_1 = -0.3$

Sensitivity parameters (c=0.3)	Placebo	Candesartan	Difference (Δ)
$l_0 = l_1 = 0$			
$a_0 = a_1 = 1$ (MAR)	83.6 (.46)	78.3 (.40)	−5.2 (−6.3,−4.0)
$a_0 = a_1 = 1.3$	83.6 (.49)	78.3 (.41)	−5.2 (−6.5,−4.0)
$a_0 = a_1 = 0.7$	83.6 (.43)	78.3 (.39)	−5.2 (−6.4,−4.1)
$l_0 = 0, l_1 = 2$			
$a_0 = a_1 = 1$	83.6 (.47)	78.9 (.41)	−4.7 (−5.9,−3.5)
$a_0 = a_1 = 1.3$	83.6 (.49)	78.9 (.43)	−4.7 (−6.0,−3.4)
$a_0 = a_1 = 0.7$	83.6 (.44)	78.9 (.40)	−4.7 (−5.9,−3.5)
$l_0 = -2, l_1 = 0$			
$a_0 = a_1 = 1$	82.1 (.46)	78.3 (.40)	−3.8 (−5.0,−2.6)
$a_0 = a_1 = 1.3$	82.1 (.49)	78.3 (.41)	−3.8 (−5.1,−2.6)
$a_0 = a_1 = 0.7$	82.1 (.44)	78.3 (.39)	−3.8 (−4.9,−2.6)
$l_0 = -2, l_1 = 2$			
$a_0 = a_1 = 1$	82.1 (.46)	78.9 (.41)	−3.3 (−4.5,−2.0)
$a_0 = a_1 = 1.3$	82.1 (.49)	78.9 (.43)	−3.3 (−4.5,−2.0)
$a_0 = a_1 = 0.7$	82.1 (.44)	78.9 (.40)	−3.3 (−4.4,−2.1)
$l_0 = -2, l_1 = -2$			
$a_0 = a_1 = 1$	82.1 (.46)	77.8 (.40)	−4.4 (−5.6,−3.1)
$a_0 = a_1 = 1.3$	82.1 (.49)	77.8 (.41)	−4.4 (−5.6,−3.1)
$a_0 = a_1 = 0.7$	82.1 (.44)	77.8 (.38)	−4.4 (−5.5,−3.2)
$l_0 = 2, l_1 = -2$			
$a_0 = a_1 = 1$	85.0 (.51)	77.8 (.40)	−7.2 (−8.5,−6.0)
$a_0 = a_1 = 1.3$	85.0 (.54)	77.8 (.41)	−7.2 (−8.5,−5.9)
$a_0 = a_1 = 0.7$	85.0 (.49)	77.8 (.39)	−7.2 (−8.4,−6.0)
$l_0 = 2, l_1 = 2$			
$a_0 = a_1 = 1$	85.1 (.51)	78.9 (.42)	−6.1 (−7.4,−4.8)
$a_0 = a_1 = 1.3$	85.0 (.54)	78.9 (.43)	−6.1 (−7.5,−4.8)
$a_0 = a_1 = 0.7$	85.0 (.49)	78.9 (.40)	−6.1 (−7.4,−4.9)
$\bar{l}_0 = -5.4, \bar{l}_1 = 0$			
$\bar{a}_0 = \bar{a}_1 = 1$	79.7 (.56)	78.3 (.40)	−1.4 (−2.7,0.0)[a]
$a_0 = a_1 = 1.3$	79.7 (.59)	78.3 (.41)	−1.4 (−2.8,0.0)
$a_0 = a_1 = 0.7$	79.7 (.54)	78.3 (.38)	−1.4 (−2.7,−0.1)
$\bar{l}_0 = 0, \bar{l}_1 = 13.3$			
$\bar{a}_0 = \bar{a}_1 = 1$	83.6 (.47)	82.0 (.68)	−1.6 (−3.2,0.0)[a]
$a_0 = a_1 = 1.3$	83.6 (.49)	82.0 (.69)	−1.6 (−3.2,0.1)
$a_0 = a_1 = 0.7$	83.6 (.44)	82.0 (.67)	−1.6 (−3.1,0.0)
$\bar{l}_0 = -3.96, \bar{l}_1 = 3.96$			
$\bar{a}_0 = \bar{a}_1 = 1$	80.7 (.51)	79.4 (.44)	−1.3 (−2.6,0.0)[a]
$a_0 = a_1 = 1.3$	80.7 (.54)	79.4 (.45)	−1.3 (−2.7,0.1)
$a_0 = a_1 = 0.7$	80.7 (.49)	79.4 (.42)	−1.3 (−2.5,0.0)

[a]Bordeline significant: *P*-value = .05.



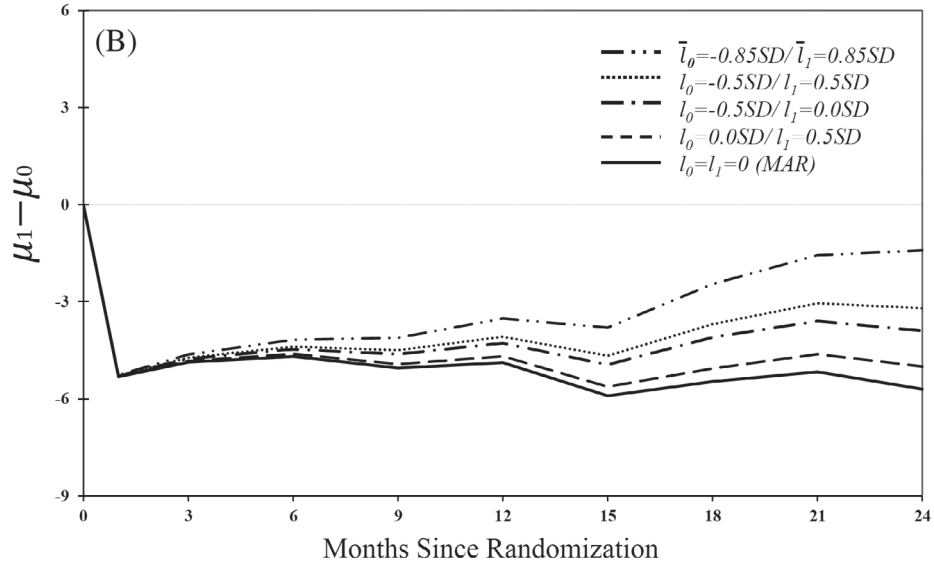


FIGURE 2 Diastolic blood pressure curves over the 24 months period for the two groups and their differences, for a range of values of sensitivity parameters

in the sensitivity analysis. We set $\bar{d}_z = -0.3, 0, .3$ and $\bar{a}_z = 1$, and find $\bar{l}_z$ indicating how much the missing data must differ from the observed data for the significance level to change. All analyses are controlled for baseline systolic blood pressure, age, and sex. The results of sensitivity analyses for DBP at 24 months are shown in Tables 1, 2, and 3. Similarly, we can estimate the DBP at each visit. We emphasize values $l_0 < 0$ and $l_1 > 0$ for the sensitivity parameters, which favor the Placebo group, to assess robustness of the effect of candesartan to unfavorable scenarios about the missing data.

Figure 2 shows the curves of DBP of the two groups for different values for l_0 and l_1, and $c = .3$, $d = 0$, and $a = 1$. The sensitivity analysis shows how the effect of candesartan over time varies by the assumptions made about the missing data. The impact of the assumed missing-data mechanism on the DBP curves increases over time, reflecting the fact that the number of the missing values that contribute to estimation of the DBP curves increases over time. The bold lines correspond to MAR, ($l = d = c = 0$, $a = 1$), and are the same as the estimates derived under standard MAR multiple imputation in SAS.

The average value of DBP at 24 months ranges from 79.7 to 87.9 for the placebo group and from 77.8 to 83.2 for the candesartan group for different missingness mechanisms. The average DBP over time is lower in the candesartan group for all the assumed scenarios in Tables 1, 2, and 3. The DBP at 24 months is also lower for the candesartan

group under all assumed scenarios; but findings become borderline or non-significant for missingness mechanisms that increasingly favor the placebo group. For example, consider the scenario where $\bar{l}_0 = -4.1$ and $\bar{l}_1 = 0$ (for $c = 0.3$, $\bar{d} = 0.3$, $\bar{a} = 1$), the subjects from a missing pattern have on average 4.1 mm Hg ($>1SD$) lower DBP than the observed subjects in the placebo group, but have the same average DBP as the observed subjects in the candesartan group; the resulting effect of candesartan at 24 month group difference in DBP is just significant, $P = .05$. For the scenario where $\bar{l}_0 = 0$ and $l_1 = 13.3$ (for $c = 0.3$, $\bar{d} = -0.3$, $\bar{a} = 1$), the subjects from a missing pattern have on average 13.3 mm Hg (>3SD) higher DBP than the observed subjects, in the candesartan group, but the same average DBP as observed subjects in the placebo group; the resulting effect of candesartan is borderline significant at 24 months, $P = .05$. The results of sensitivity analysis are also impacted by the magnitude of d, with the estimate of DBP at 24 months being lower when $d = -0.3$ (ie, 30% lower visit-to-visit associations among subjects in a missing pattern versus observed subjects), and higher when $d = 0.3$. The a parameter does not impact the point estimates, but it has an impact on the estimate of the posterior variance, being higher when $a > 1$ and lower when $a < 1$. Under MAR the DBP at 24 months was 5.7 mm Hg (95% credible interval [−7.1;−4.4]) lower in the candesartan group, at 78.6 mm Hg, compared to the placebo group, 84.3 mm Hg. Furthermore, the average DBP at 24-months in candesartan group was in the recommended healthy range of less than 80 mm Hg for all sensitivity analysis, except for one extreme scenario.

Finally, to assess the effects of perturbations of the sensitivity parameters around MAR on the inference about the treatment effect we introduce a sensitivity index (SI) statistics defined as:

$$SI(\omega) = \frac{\Delta_{MNAR}(\omega) - \Delta_{MAR}(\omega_0)}{\Delta_{MAR}(\omega_0)} \times 100\%.$$

$SI(\omega)$ captures the relative difference on the treatment effect $\Delta_{MNAR}(\omega)$ estimated under a specific MNAR mechanism indexed by $\omega = (c, l_0, l_1, d_0, d_1, a_0, a_1)$ compared to the treatment effect $\Delta_{MAR}(\omega_0)$ estimated under the MAR $\omega_0 = (0, 0, 0, 0, 0, 1, 1)$. We vary the set of sensitivity parameters (l_0, l_1), (d_0, d_1), and (a_0, a_1) from ω_0 one at a time to assess the impact of each set; the coefficient of variation is set at $c = 0.3$. The summary of the posterior distribution of $SI(\omega)$ for alternative perturbations of (l_0, l_1), (d_0, d_1), and (a_0, a_1) is shown in Figure 3.

The sensitivity parameters that have the stronger impact on the magnitude of the treatment effect Δ are (l_0, l_1) and (d_0, d_1), whereas (a_0, a_1) have no impact on the point estimate. As expected, the more the sensitivity parameters deviate from ω_0, the bigger the change on the estimate of treatment effect compared to the estimate under MAR. In addition, the parameters corresponding to the placebo group l_0 and d_0 have a bigger impact compared to l_1 and d_1 respectively, due to the fraction of the missing data being higher in the placebo group compared to the treatment group. Thus, even if the missingness mechanism is similar between two groups (ie, $l_0 = l_1 = 2$, or $d_0 = d_1 = 0.3$) the estimate on the treatment effect would still be different from the estimate under a MAR, and vary for different values of l or d parameters. For example, compared to the estimate under MAR, the treatment effect when $l_0 = l_1 = -2$ is reduced by 19.5% but increase by 19.7% when $l_0 = l_1 = 2$.

5.3 | Summary of results

In summary, the differences in the DBP between two groups over the entire study are robust to different missingness scenarios. The difference in the variance parameters between subjects from a missing patterns and observed subjects (measured by a) does not have an impact on the estimate of the mean DBP, but it effects the corresponding standard error and the 95% credible interval. As expected, when subjects from a missing pattern have lower SD than the observed subjects (ie, $a = 0.7$) the overall standard error is lower and vice versa. The difference on the strength of lag-l autoregression coefficient between the subjects from a missing pattern and observed subjects (measured by d) does have an impact on the DBP at 24 months. In TROPHY, if the lag-l coefficient is lower or $d < 0$, the overall DBP estimates at 24 months are lower compare to when $d > 0$, other sensitivity parameters being the same. Thus, the group differences at 24 months are sensitive to the dropout mechanism, varying from −1.3 to −9.7 mm Hg for the scenarios shown in Tables 1, 2, and 3. Under MAR, a two-year treatment with candesartan reduces the DBP at 24 months by 5.7 mm Hg. In addition, the effect of candesartan treatment is robust around a region of the MAR mechanism. It would take large differences on the DBP value between dropout and observed subjects favoring placebo for the effect of treatment to become borderline significant.

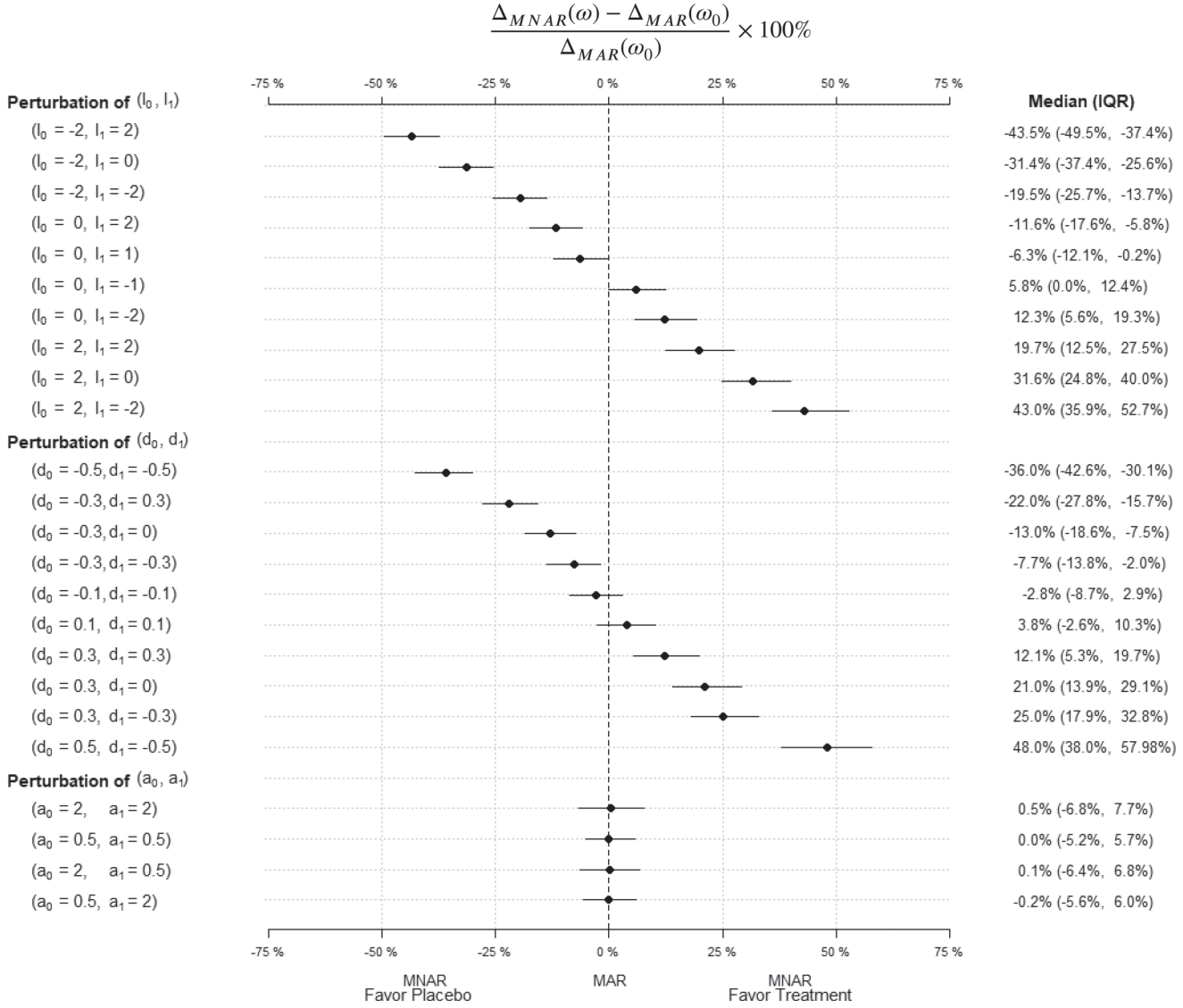


FIGURE 3 Relative % change on treatment effect Δ for alternative perturbations of the sensitivity parameters $\omega = (c, l_0, l_1, d_0, d_1, a_0, a_1)$ around the MAR $\omega_0 = (0, 0, 0, 0, 0, 1, 1)$

6 | SIMULATION STUDIES

In this section, we describe simulation studies to assess the performance of our proposed Bayesian model under a variety of missingness mechanisms and also compare it to δ-adjusted multiple imputation (MI) method.[25] One thousand data sets were simulated using similar design as in the TROPHY study. Specifically, for each treatment group the data for the observed patterns were generated using distributions similar to the observed data in the TROPHY study. First, n=391 observations for the treatment group and n=381 for the control group where the generated from a normal distribution with values truncated to be lower than 91, which was the maximum baseline DBP value in TROPHY. Then the $Y_2, Y_3, \ldots \ldots, Y_K$ were generated sequentially for each group using $Y_2|Y_1 \sim N(\mu_{2|1}, \sigma^2_{2|1})$ and $Y_k|Y_{k-1}, Y_{k-2} \sim N(\mu_{k|k^-}, \sigma^2_{k|k^-})$ for $k = 2, \ldots \ldots K$, where the mean and variance parameters were set at the corresponding estimated value from the TROPHY data. To limit computations no covariates were included and we set $k = 1, 2, \ldots, 5$, where Y_1 corresponds to baseline data, and Y_2, Y_3, Y_4, and Y_5 correspond to 6, 12, 18, and 24-months follow-ups. The dropout indicators at time $k = 2, 3, 4$, and 5 for each group were generated using $D_k \sim Bernoulli(p_k)$ where p_k was derived based on $logit(p_2) = \gamma_{02} + \gamma_{12} * Y_1$ and $logit(p_k|D_{k-1} = 0) = \gamma_{0k} + \gamma_{1k} * Y_{k-1} + \gamma_{2k} * Y_{k-2}$ for $k = 3, 4$, and 5 with γ parameters estimated using TROPHY data. The data with $D_k = 1$ were considered as dropouts at visit k. Next, we generate missing values

TABLE 4 Simulation studies under MAR

	Estimate(SE_{Sim})[$\overline{SE}$]		
Method	**Control**	**Treatment**	**Difference (Δ)**
Baseline			
Full Data	84.850(.219)[.213]	84.845(.213)[.210]	−0.005(.304)[.298]
δ-adjusted MI	84.850(.219)[.213]	84.845(.213)[.210]	−0.005(.304)[.298]
Bayesian	84.849(.218)[.213]	84.845(.213)[.209]	−0.004(.304)[.298]
Follow-up 1			
Full Data	83.229(.399)[.397]	78.598(.364)[.359]	−4.631(.551)[.546]
δ-adjusted MI	83.233(.415)[.411]	78.597(.373)[.365]	−4.636(.568)[.558]
Bayesian	83.233(.414)[.410]	78.598(.374)[.364]	−4.635(.567)[.548]
Follow-up 2			
Full Data	83.526(.365)[.358]	78.683(.362)[.361]	−4.842(.519)[.513]
δ-adjusted MI	83.525(.404)[.397]	78.681(.374)[.374]	−4.843(.553)[.547]
Bayesian	83.523(.404)[.400]	78.681(.372)[.373]	−4.842(.551)[.546]
Follow-up 3			
Full Data	82.882(.388)[.390]	78.051(.356)[.361]	−4.831(.526)[.531]
δ-adjusted MI	82.888(.482)[.471]	78.050(.378)[.382]	−4.838(.609)[.605]
Bayesian	82.890(.475)[.494]	78.051(.377)[.382]	−4.839(.604)[.625]
Follow-up 4			
Full Data	82.884(.346)[.351]	78.456(.371)[.373]	−4.427(.493)[.499]
δ-adjusted MI	82.897(.491)[.450]	78.460(.409)[.411]	−4.437(.619)[.593]
Bayesian	82.896(.484)[.493]	78.461(.406)[.415]	−4.434(.613)[.645]

for dropouts using $f(Y_{zk}|\underline{Y}_{zk-1}, R = r) = N(\mu^{(r)}_{zk|k^-}, \sigma^{2(r)}_{zk|k^-})$, for $k > r$ where $\mu^{(r)}_{zk|k^-}$ and $\sigma^{2(r)}_{zk|k^-}$ are determined following (4) and the sensitivity parameters. The full generated data (as if there were no dropouts) were used to estimate parameters of interest, which were used as the benchmark for evaluating the performance of our Bayesian model and the δ-adjusted method.

For each simulated data set we derive the parameter estimates based on the proposed Bayesian model and δ-adjusted MI method. The δ-adjusted imputation was implemented using PROC MI in SAS for each group and each missing pattern with MNAR option. The algorithm described in Ratitch et al[25] was used, where missing values were multiply-imputed sequentially for each Y_t based on previous $\underline{Y}_{t-1}$ (observed and imputed) using a MAR model with a δ shift value added at each imputed data. The final estimates were derived based on 25 imputed data set using PROC MIANALYZE. In addition, we also estimated same parameters using the full data (including the dropouts). The estimates based on our model and the δ-adjusted MI were compared with the estimates of the full data across all 1000 simulated data set, and the bias, standard error and the nominal 95% coverage rate were calculated. The results for a range of sensitivity parameters are shown in Table 4 for MAR and Tables 5,6,7,8,9 for MNAR. In Table 4 we show the estimates using our Bayesian approach, δ-adjusted MI (with 25 imputed data set and $\delta = 0$), and based on the full generated data as if there were no dropouts. The point estimates at each visit are the same among three methods, the standard error from the 1000 simulations (SE_{Sim}) based on our Bayesian model and δ-adjusted MI are similar, but lower than the standard error based on the full data, reflecting increased information from the missing data. The average standard error ($\overline{SE}$) for our Bayesian method are closer to corresponding SE_{Sim} when compared to the δ-adjusted MI method, showing a better performance of our Bayesian method in estimating the standard error.

In Tables 5,6,7,8 we show point estimate, bias and 95% coverage at the last visit under alternative MNAR missingness mechanisms (varying the sensitivity parameters l_0, l_1, d_0, d_1, a_0, a_1, and $c = .3$). In Table 5 we set $d_0 = d_1 = 0$, in Table 6 $d_0 = d_1 = 0.3$, and Table 7 $d_0 = d_1 = -0.3$, then within each table (l_0, l_1) and (a_0, a_1) are varied. In Table 8 we

TABLE 5 Simulation studies under alternative dropout mechanisms with $d_0 = d_1 = 0$

Sensitivity parameters (c=0.3)	**Estimate(*Bias*)[*Coverage Probability*]**		
(l_0, l_1) (d_0, d_1) (a_0, a_1)	**Control**	**Treatment**	**Difference (Δ)**
(0,0) (0,0) (1,1)[a]			
Bayesian	82.90(.012)[95.1]	78.46(.005)[95.4]	−4.43(−.007)[95.8]
δ-adjusted MI	82.90(.014)[93.2]	78.46(.002)[95.6]	−4.44(−.012)[93.3]
(0,2) (0,0) (1,1)			
Bayesian	82.90(.010)[94.8]	79.02(−.004)[96.2]	−3.87(−.014)[96.0]
δ-adjusted MI	82.90(.011)[93.0]	79.02(−.003)[95.4]	−3.87(−.014)[93.4]
(−2,0) (0,0) (1,1)			
Bayesian	81.40(.017)[96.2]	78.46(.003)[95.8]	−2.94(−.013)[96.7]
δ-adjusted MI	81.40(.020)[94.6]	78.46(.002)[95.0]	−2.94(−.018)[95.5]
(−2,2) (0,0) (1,1)			
Bayesian	81.40(.016)[96.4]	79.02(−.004)[96.0]	−2.37(−.020)[96.4]
δ-adjusted MI	81.40(.018)[94.8]	79.02(−.006)[95.9]	−2.38(−.024)[94.9]
(−2,2) (0,0) (.7,.7)			
Bayesian	81.40(.016)[95.8]	79.03(−.003)[95.1]	−2.37(−.019)[95.6]
δ-adjusted MI	81.40(.015)[95.0]	79.03(−.002)[95.9]	−2.37(−.017)[95.2]
(−2,2) (0,0) (1.3,1.3)			
Bayesian	81.40(.017)[97.2]	79.02(−.003)[96.8]	−2.37(−.020)[97.0]
δ-adjusted MI	81.40(.020)[95.4]	79.02(−.005)[96.0]	−2.38(−.025)[95.5]

[a]Data missing at random.

TABLE 6 Simulation studies under alternative dropout mechanisms with $d_0 = d_1 = 0.3$

Sensitivity parameters (c=0.3)	**Estimate(*Bias*)[*Coverage Probability*]**		
(l_0, l_1) (d_0, d_1) (a_0, a_1)	**Control**	**Treatment**	**Difference (Δ)**
(0,0) (.3,.3) (1,1)			
Bayesian	83.44(.161)[95.3]	78.74(.031)[94.9]	−4.69(−.130)[95.1]
δ-adjusted MI	82.90(−.430)[81.5]	78.46(−.255)[91.4]	−4.44(.176)[92.9]
(0,2) (.3,.3) (1,1)			
Bayesian	83.43(.160)[95.0]	79.38(.034)[95.6]	−4.06(−.126)[95.0]
δ-adjusted MI	82.90(−.434)[80.8]	79.02(−.330)[93.3]	−3.88(.105)[93.3]
(−2,0) (.3,.3) (1,1)			
Bayesian	81.73(−.016)[97.8]	78.74(.032)[94.6]	−2.99(.048)[96.0]
δ-adjusted MI	81.40(−.217)[92.3]	78.46(−.254)[91.7]	−2.94(−.038)[95.3]
(−2,2) (.3,.3) (1,1)			
Gaussian: Bayesian	81.75(.131)[97.1]	79.36(.010)[96.9]	−2.39(−.120)[96.8]
δ-adjusted MI	81.40(−.220)[92.3]	79.02(−.326)[89.2]	−2.37(−.106)[95.3]
Gamma: Bayesian	81.75(.120)[97.4]	79.36(.005)[96.8]	−2.39(−.115)[97.3]
δ-adjusted MI	81.39(−.237)[91.5]	79.04(−.313)[87.2]	−2.35(−.075)[93.3]
(−2,2) (.3,.3) (.7,.7)			
Bayesian	81.75(.131)[96.4]	79.36(.010)[95.9]	−2.39(−.121)[96.4]
δ-adjusted MI	81.40(−.217)[92.5]	79.02(−.326)[88.7]	−2.38(−.109)[95.2]
(−2,2) (.3,.3) (1.3,1.3)			
Bayesian	81.75(.130)[97.8]	79.36(.011)[97.2]	−2.39(−.120)[97.8]
δ-adjusted MI	81.40(−.218)[92.7]	79.02(−.324)[89.1]	−2.37(−.106)[95.1]

TABLE 7 Simulation studies under alternative dropout mechanisms with $d_0 = d_1 = -0.3$

Sensitivity parameters (c=0.3)	**Estimate(*Bias*)[*Coverage Probability*]**		
(l_0, l_1) (d_0, d_1) (a_0, a_1)	**Control**	**Treatment**	**Difference (Δ)**
(0,0) (−.3,−.3) (1,1)			
Bayesian	82.43(−.103)[93.4]	78.22(−.013)[93.9]	−4.21(.090)[93.7]
δ-adjusted MI	82.90(.366)[83.7]	78.46(.214)[91.9]	−4.44(−.152)[92.4]
(0,2) (−.3,−.3) (1,1)			
Bayesian	82.43(−.119)[93.5]	78.73(−.043)[94.1]	−3.70(.076)[94.2]
δ-adjusted MI	82.90(.364)[84.5]	79.02(.263)[90.9]	−3.88(−.101)[93.8]
(−2,0) (−.3,−.3) (1,1)			
Bayesian	81.13(−.104)[95.2]	78.22(−.012)[94.3]	−2.91(.091)[94.6]
δ-adjusted MI	81.40(.185)[94.1]	78.46(.217)[91.3]	−2.94(.033)[94.9]
(−2,2) (−.3,−.3) (1,1)			
Bayesian	81.13(−.091)[94.3]	78.74(−.016)[95.6]	−2.38(.075)[96.0]
δ-adjusted MI	81.40(.182)[93.9]	79.02(.265)[89.9]	−2.37(.083)[95.5]
(−2,2) (−.3,−.3) (.7,.7)			
Bayesian	81.13(−.090)[93.8]	78.74(−.017)[94.7]	−2.38(.074)[95.1]
δ-adjusted MI	81.40(.185)[94.1]	79.02(.266)[90.7]	−2.38(.081)[95.4]
(−2,2) (−.3,−.3) (1.3,1.3)			
Bayesian	81.13(−.091)[95.5]	78.74(−.015)[96.6]	−2.38(.076)[96.7]
δ-adjusted MI	81.40(.185)[94.0]	79.02(.266)[90.4]	−2.38(.080)[94.8]

evaluate the performance of each method by varying only (d_0, d_1) parameters and setting $l_0 = l_1 = 0$ and $a_0 = a_1 = 1$. When $d_0 = d_1 = 0$ the results based on our approach are similar to those based on the δ-adjusted MI. The nominal 95% coverages in Tables 4 and 5 are close to 95% ranging from 93.4%to 97.8%. However, when the d_0 and d_1 are different from zero, the results based on our proposed model have lower bias and better 95% coverage than the δ-adjusted MI. When there are differences $(d \neq 0)$ in the lag-associations between dropouts and observed subjects the δ-adjusted MI performed poorly, with nominal 95% coverage as low as 78.6% (Tables 6,7,8). The simulation results confirm the findings from the sensitivity analysis in TROPHY data that the inferences are effected from l, d, and a parameters, where l and d have an impact on the point estimate and a having an impact on the standard error but not on the point estimate.

Finally, our model assumes that the distribution $f(Y_{zk}|\underline{Y}_{zk-1}, R = r)$ is normal. For the observed data patterns $(r \geq k)$ this assumption is testable based on the available data, however for the missing-data patterns $(r < k)$ the normality assumption is not testable based on the available data. To assess the robustness to minor perturbation from the normal distribution on the missing data, we perfom simulations where the missing data are generated based on a truncated $t - distribution$ with four degrees of freedom, truncated between 60 and 120. Table 9 shows the simulations results for same scenarios as in Table 8, but when the true distribution of the missing values is the truncated $t - distribution$. The results based on the Bayesian model in Tables 8 and 9 are similar, indicating robustness to minor perbutations from the normality assumption in the missing patterns. The δ-adjustment MI also showed good robustness, though there was a small decrease in the coverage probability.

7 | CONCLUDING REMARKS

We have presented a Bayesian pattern-mixture model for longitudinal data with potentially future-dependent MNAR dropout. The identifying parameters, $\tilde{\lambda}_k^{(r)}$, $\tilde{\delta}_{lk}^{(r)}$, and $\tilde{\psi}_k^{(r)}$, are defined for each group as follows: $\tilde{\lambda}_k^{(r)}$ represents the

TABLE 8 Simulation studies under alternative dropout mechanisms with $l_0 = l_1 = 0$ and $a_0 = a_1 = 1$

Sensitivity parameters (c=0.3)	**Estimate(*Bias*)[*Coverage Probability*]**		
(l_0, l_1) (d_0, d_1) (a_0, a_1)	**Control**	**Treatment**	**Difference (Δ)**
(0,0) (.3,−.3) (1,1)			
Bayesian	83.46(.118)[96.2]	78.24(−.009)[94.6]	−5.22(−.127)[96.1]
δ-adjusted MI	82.90(−.441)[80.7]	78.46(.214)[92.0]	−4.44(.656)[78.6]
(0,0) (.3, 0) (1,1)			
Bayesian	83.46(.118)[96.1]	78.46(.005)[95.9]	−5.00(−.115)[96.6]
δ-adjusted MI	82.90(−.439)[80.4]	78.46(.003)[95.2]	−4.44(.442)[86.5]
(0,0) (0,−.3) (1,1)			
Bayesian	82.89(.000)[94.9]	78.24(−.009)[94.7]	−.4.66(.009)[95.7]
δ-adjusted MI	82.90(.007[91.6]	78.46(.217)[91.9]	−.4.44(.210)[92.4]
(0,0) (0, .3) (1,1)			
Bayesian	82.90(.001)[95.0]	78.73(.018)[96.4]	−.4.16(.017)[96.2]
δ-adjusted MI	82.90(.009)[92.0]	78.46(−.257)[91.3]	−.4.44(−.265)[91.2]
(0,0) (−.3, 0) (1,1)			
Bayesian	82.44(−.108)[93.1]	78.46(.003)[96.1]	−.3.97(.112)[95.9]
δ-adjusted MI	82.90(.356)[84.8]	78.46(.002)[94.6]	−.4.44(−.354)[90.6]
(0,0) (−.3,.3) (1,1)			
Bayesian	82.43(−.109)[93.2]	78.73(.018)[96.3]	−.3.70(.126)[96.2]
δ-adjusted MI	82.90(.357)[84.2]	78.46(−.255)[91.8]	−.4.44(−.612)[82.3]

TABLE 9 Simulation studies under alternative dropout mechanisms with $l_0 = l_1 = 0$, $a_0 = a_1 = 1$ and missing data following a truncated $t - distribution$ distribution with 4 degrees of freedom

Sensitivity parameters (c=0.3)	**Estimate(*Bias*)[*Coverage Probability*]**		
(l_0, l_1) (d_0, d_1) (a_0, a_1)	**Control**	**Treatment**	**Difference (Δ)**
(0,0) (.3,−.3) (1,1)			
Bayesian	83.46(.090)[96.3]	78.24(−.059)[94.1]	−.5.22(−.149)[95.9]
δ-adjusted MI	82.88(−.485)[79.6]	78.47(.176)[92.9]	−.4.41(.661)[76.7]
(0,0) (.3, 0) (1,1)			
Bayesian	83.46(.091)[96.5]	78.46(−.048)[94.7]	−.5.00(−.140)[96.1]
δ-adjusted MI	82.89(−.483)[76.0]	78.47(−.037)[95.4]	−.4.41(.445)[84.4]
(0,0) (0,−.3) (1,1)			
Bayesian	82.90(−.016)[95.1]	78.24(−.059)[94.4]	−.4.66(.043)[95.3]
δ-adjusted MI	82.89(−.026[91.4]	78.47(.176)[92.8]	−.4.41(.202)[91.2]
(0,0) (0, .3) (1,1)			
Bayesian	82.90(−.016)[95.4]	78.73(−.036)[95.7]	−.4.16(−.021)[95.7]
δ-adjusted MI	82.89(−.026)[90.8]	78.47(−.297)[87.7]	−.4.41(−.271)[91.4]
(0,0) (−.3, 0) (1,1)			
Bayesian	82.43(−.129)[92.6]	78.46(−.048)[95.5]	−.3.97(.081)[95.9]
δ-adjusted MI	82.89(.322)[85.5]	78.47(−.036)[95.4]	−.4.41(−.358)[89.7]
(0,0) (−.3,.3) (1,1)			
Bayesian	82.44(−.128)[92.5]	78.73(−.037)[95.8]	−.3.70(.092)[96.2]
δ-adjusted MI	82.88(.320)[85.6]	78.47(−.297)[88.1]	-4.41(−.618)[80.2]

absolute difference on the conditional mean (conditioned on the previous visits $1, 2, \ldots, k-1$ at the average value $\bar{y}_1^{(\geq k)}, \bar{y}_2^{(\geq k)}, \ldots, \bar{y}_{k-1}^{(\geq k)}$ and covariates at average value $\bar{x}$), between subjects from missing-data pattern r at visit k with the observed subjects at visit k; $\tilde{\delta}_{lk}^{(r)}$ represents the relative difference on the lag-l autoregressive coefficient between the subjects from missing-data in pattern r at visit k with the observed subjects at visit k; $\psi_k^{(r)}$ represents the ratio of variances between the subjects from missing-data pattern r at visit k with observed subjects at visit k, conditioned on the previous visits $1, 2, \ldots, k-1$ and covariates. Sensitivity analyses are performed using different prior distributions for $\tilde{\lambda}_k^{(r)}$, $\tilde{\delta}_k^{(r)}$, and $\tilde{\psi}_k^{(r)}$. Even though the distributions of $\tilde{\lambda}_k^{(r)}$, $\tilde{\delta}_{lk}^{(r)}$, and $\tilde{\psi}_k^{(r)}$ are unknown, it is possible for a subject matter expert to give a range and then explore the sensitivity of statistical inferences over that a range. The new parameterization is based on the PMM framework and does not use an explicit model for missing data, which is hard to correctly specify when the number of missing-data patterns is large. As the number of follow-up visits increases, so does the number of the sensitivity parameters; We reduced the dimensionality of the sensitivity space by modeling $\tilde{\lambda}_k^{(r)}$, $\tilde{\delta}_{lk}^{(r)}$ as normal and $\tilde{\psi}_k^{(r)}$ as log-normal, reducing the set of the sensitivity parameters to the means and coefficients of variation of these distributions. Our proposed parameterization creates a flexible class of MNAR missing-data mechanisms that allows for differences between dropouts and observed subjects in the mean, variance, and visit-to-visit association, and it contains MAR as a special case. Sensitivity analysis can be performed around a region corresponding to MAR for a range of values specified by a subject matter expert, as well as providing tipping point sensitivity analysis.

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DATA AVAILABILITY STATEMENT

Data subject to third party restrictions

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REFERENCES

1. Little R. Pattern-mixture models for multivariate incomplete data. *J Am Stat Assoc*. 1993;88:125-134.
2. Little R, Rubin D. *Statistical Analysis with Missing Data*. 3rd ed. Hoboken, NJ: John Wiley; 2019.
3. Rotnitzky A, Robins J, Scharfstein D. Semiparametric regression for repeated outcomes with nonignorable nonresponse. *J Am Stat Assoc*. 1998;93:1321-1339.
4. Scharfstein D, Rotnitzky A, Robins J. Adjusting for non-ignorable drop-out using semiparametric nonresponse models (with Discussion). *J Am Stat Assoc*. 1999;94:1096-1146.
5. Scharfstein D, Daniels M, Robins J. Incorporating prior beliefs about selection bias into the analysis of randomized trials with missing outcomes. *Biostatistics*. 2003;4(4):495-512.
6. Wu M, Carroll R. Estimation and comparison of changes in the presence of informative right censoring by modeling the censoring process. *Biometrics*. 1988;44:175-188.
7. Guo W, Ratcliffe S, Ten Have T. A random pattern-mixture model for longitudinal data with dropouts. *J Am Stat Assoc*. 2004;99:929-937.
8. Kenward M, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. *Biometrika*. 2003;90:53-71.
9. Roy J, Daniels M. A general class of pattern-mixture models for nonignorable dropout with many possible dropout times. *Biometrics*. 2008;64:538-545.
10. Zhang Y, Tang N, Qu A. Imputed factor regression for high-dimensional block-wise missing data. *Stat Sin*. 2020;30:631-651.
11. Wang C, Daniels M, Scharfstein D, Land S. A Bayesian shrinkage model for incomplete longitudinal binary data with application to the breast cancer prevention trial. *J Am Stat Assoc*. 2010;105(492):1333-1346.
12. Scharfstein D, McDermoot A, Diaz I, Carone M, Lunardon N, Turkoz I. Global sensitivity analysis for repeated measures studies with informative drop-out: a semi-parametric approach. *Biometrics*. 2018;74:207-219.
13. Little R. Modeling the dropout mechanism in repeated measures studies. *J Am Stat Assoc*. 1995;90:1113-1121.
14. Carpenter J, Roger J, Kenward M. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. *Biopharm Stat*. 2013;23(6):1352-1371.
15. Kaçiroti N, Raghunathan T. Bayesian sensitivity analysis of incomplete data: bridging pattern-mixture and selection models. *Stat Med*. 2014;33(27):4841-4857.
16. Wang C, Daniels M. A note on MNAR, identifying restrictions, model comparisons, and sensitivity analysis in pattern mixture models with and without covariates for incomplete data. *Biometrics*. 2011;67:810-818.
17. Linero A, Daniels M. A flexible Bayesian approach to monotone missing data in longitudinal studies with nonignorable missingness with application to an acute schizophrenia clinical trial. *J Am Stat Assoc*. 2015;110:45-55.

18. Daniels M, Hogan J. *Missing Data in Longitudinal Studies: Strategies for Bayesian Modeling and Sensitivity Analysis*. Boca Raton, FL: Chapman & Hall; 2007.
19. Molenberghs G, Kenward M. *Incomplete Data in Clinical Studies*. Chichester: John Wiley; 2007.
20. National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education*. Washington, DC: The National Academies Press; 2010.
21. Julius S, Nesbitt S, Egan B, et al. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med*. 2006;354:1685-1697.
22. Julius S, Kaçiroti N, Nesbitt S, Egan BM, Michelson EL, for the Trial of Preventing Hypertension (TROPHY) Investigators. TROPHY study: outcomes based on the JNC 7 definition of hypertension. *J Am Soc Hypertens*. 2008;2(1):39-43.
23. Whelton P, Carey R, Aronow W, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71(19):2199-2169.
24. Byrd J, Brook R. Hypertension. *Ann Intern Med*. 2019;170(9):ITC65-ITC80.
25. Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. *Pharm Stat*. 2013;12(6):337-347.
26. Wang H, Feng X. Multiple imputation for, m-regression with censored covariates. *J Am Stat Assoc*. 2012;107:194-204.
27. Tang M, Tang N, Zhao P, Zhu H. Efficient robust estimation for linear models with missing response at random. *Scand J Stat*. 2018;45:366-381.
28. Mehlum M, Liestøl K, Julius S, et al. Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. *Eur Heart J*. 2018;39(24):2243-2251.
29. Levitan E, Kaçiroti N, Oparil S, Julius S, Muntner P. Blood pressure measurement device, number and timing of visits, and intra-individual visit-to-visit variability of blood pressure. *J Clin Hypertens*. 2012;14(11):744-750.
30. Kaçiroti N, Raghunathan T, Taylor J, Julius S. A Bayesian model for time-to-event data with informative censoring. *Biostatistics*. 2012;13(2):341-354.
31. Ma G, Troxel A, Heitjan D. An index of local sensitivity to nonignorable drop-out in longitudinal modeling. *Stat Med*. 2005;24:2129-2150.
32. Molenberghs G, Michiels B, Kenward M, Diggle P. Monotone missing data and pattern-mixture models. *Statistica Neerlandica*. 1998;52:153-161.
33. Rubin D. Bayesian bootstrap. *Ann Stat*. 1981;9(1):130-134.
34. Demirtas H, Schafer J. On the performance of random-coefficient pattern-mixture models for non-ignorable drop-out. *Stat Med*. 2003;22:2553-2575.
35. Kaçiroti N, Raghunathan T, Schork M, Clark N. A Bayesian model for longitudinal count data with non-ignorable dropout. *J R Stat Soc Ser C Appl Stat*. 2008;57:521-534.
36. Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. *J Biopharm Stat*. 2009;19(6):1085-1098.
37. Gelman A, Rubin D. Inference from iterative simulation using multiple sequences. *Stat Sci*. 1992;7:457-511.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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