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Accounting for not-at-random missingness through imputation stacking

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Summary

Not-at-random missingness presents a challenge in addressing missing data in many health research applications. In this paper, we propose a new approach to account for not-at-random missingness *after multiple imputation* through weighted analysis of stacked multiple imputations. The weights are easily calculated as a function of the imputed data and assumptions about the not-at-random missingness. We demonstrate through simulation that the proposed method has excellent performance when the missingness model is correctly specified. In practice, the missingness mechanism will not be known. We show how we can use our approach in a sensitivity analysis framework to evaluate the robustness of model inference to different assumptions about the missingness mechanism, and we provide R package *StackImpute* to facilitate implementation as part of routine sensitivity analyses. We apply the proposed method to account for not-at-random missingness in human papillomavirus test results in a study of survival for patients diagnosed with oropharyngeal cancer.

KEYWORDS:
chained equations multiple imputation, fully conditional specification, not-at-random missingness, sensitivity analysis, stacked imputation

1 Introduction

Multiple imputation is a popular and convenient strategy for addressing missing data in modern health research.[1] One common strategy for obtaining imputations of the missing data involves filling in values for each variable with missingness one-by-one as part of an iterative algorithm.[2,3] In this approach, the problem of missing data handling translates into specification and estimation of the imputation distribution used to fill in the missing values for each variable. Multiple versions of the filled-in data are generated, and the goal data analysis is performed using each imputed dataset separately and combined using multiple imputation combining rules.[4] This general missing data handling approach, called chained equations imputation or fully conditional specification, can be easily implemented using available statistical software. A robust statistical literature provides guidance for implementation in many common data analysis scenarios, but the majority of the statistical development and software rely on the key assumption that missingness is unrelated to unobserved data given observed data, called missing at random (MAR).

In many practical data settings, however, the restrictive MAR assumption may not hold. In the particular setting of health research, for example, results of medical tests may often be available for only a subset of patients. Symptom-informed medical testing can induce a relationship between whether a test is administered and the test result, even after adjusting for other observed data. When missingness relates to unobserved information, called missing not at random (MNAR), use of standard imputation strategies that rely on MAR assumptions can often result in biased inference.[4]

Several researchers have developed modifications to the chained equations imputation procedure that incorporate corrections for MNAR missingness. Tompsett et al. (2018) proposed imputing each variable with missingness using a model that also adjusts for the missingness indicators for the *other* variables.[5] The relationship between missingness and the variable being imputed is incorporated through a fixed offset in the imputation model with a corresponding sensitivity parameter. The random indicator method proposed in Jolani (2012) avoids the use of fixed sensitivity parameters, but existing software implicitly assumes a logistic regression model for missingness with main effects only, which may be violated in practice. Both methods rely on some degree of approximation in the distribution of missing values given observed values.[6]

Additionally, these approaches to handling MNAR missingness assume that the analyst fitting the target model is also the analyst imputing the data, but this may not always be the case. Carpenter et al. (2007) provides a sensitivity analysis approach that re-weights parameter estimates from multiple imputations generated under MAR assumptions, with the structure of the weights used to account for the MNAR missingness.[7] This method can perform well in settings where the MNAR missingness is weak, but several authors have noted that this method can perform poorly when MNAR missingness is strong.[8] Corrections to this method provided in Smuk (2015) only partially address this issue.[9]

In this paper, we propose a new approach for addressing not-at-random missingness that takes advantage of recent advances in the area of stacked multiple imputations.[10] In the proposed approach, multiple imputations obtained under MAR assumptions are stacked and augmented with a weight related to the assumed MNAR missingness mechanism. Unlike the related approach in Carpenter et al. (2007), the proposed method defines weights separately for each subject and uses weights to obtain parameter estimates rather than solely for aggregating estimates across multiple imputations.[7] When all models are correctly specified, we can obtain valid estimates of parameters of interest (e.g. means, regression model parameters, etc.) by performing a weighted version of the target analysis on the stacked multiple imputations. We describe several strategies for obtaining corresponding standard errors based on previous work by Beesley and Taylor (2020) and Bernhardt (2019).[10,11] We demonstrate through simulation that the proposed method has excellent performance when the missingness model is correctly specified. In practice, the missingness mechanism will not be known. We show how we can use our approach in a sensitivity analysis framework to evaluate the robustness of model inference to different MNAR assumptions and describe how existing methods for eliciting sensitivity parameters can be adapted and applied. We apply the proposed method to account for potential MNAR missingness in human papillomavirus (HPV) test results in a study of survival for patients diagnosed with oropharyngeal cancer. We also provide R package *StackImpute* to facilitate implementation as part of routine sensitivity analyses to deviations from MAR.

2 Imputation stacking approach for single variable MNAR missingness

2.1 Notation and assumptions

Let Z be a $n \times p$ matrix containing p variables measured on n independent subjects such that the first k variables in Z are missing for some subjects and the last $p-k$ variables (denoted W) are fully-observed for all subjects. Let R_{ij} be an indicator for whether variable j is measured for subject i in the data. Our goal is to obtain multiple imputations of the missing values in Z, with which we will perform some target analysis. For example, we may be interested in the mean of the j^{th} variable in Z or a regression model of the first variable on the others. Throughout, let $Z_{i.}$ denote data for the i^{th} subject, and let $Z_{.j}$ denote the j^{th} variable. Define rows and columns in matrices R and W similarly. Let $Z_{i,-j}$ denote the elements in $Z_{i.}$ excluding the j^{th} variable. We will assume data are independent across subjects.

We imagine the missingness pattern R_{ij} observed in the data is a *data realization* of a corresponding *random variable*, denoted $\mathcal{R}_{ij}$. Collectively, we call these random indicators $\mathcal{R}$. Under missing at random (MAR) assumptions, the joint distribution of $\mathcal{R}$ may depend only on fully-observed data in Z, and the mechanism generating data missingness can be ignored during data imputation.[4] However, it is possible that missingness depends on unobserved information in Z, called missing not at random (MNAR). Here, we consider a particular generalization of the MAR setting where the first variable in Z, denoted $Z_{.1}$, may be MNAR. For an extension of these methods under multiple variable MNAR missingness, see **Supplementary Section A**.

Suppose we partition the joint model for missingness as

$$f(\mathcal{R}_{i1}, \dots, \mathcal{R}_{ik} | Z_{i.}) = f(\mathcal{R}_{i2}, \dots, \mathcal{R}_{ik} | Z_{i.}, \mathcal{R}_{i1}) f(\mathcal{R}_{i1} | Z_{i.}).$$

where f denotes the distribution function for the corresponding variables. We will assume the following:

1. $Z_{i2}, \dots, Z_{ik}$ are MAR, with $f(\mathcal{R}_{i2}, \dots, \mathcal{R}_{ik} | Z_{i.}, \mathcal{R}_{i1}) = f(\mathcal{R}_{i2}, \dots, \mathcal{R}_{ik} | W_{i.})$.

2. Z_{i1} may be MNAR, with $f(\mathcal{R}_{i1}|Z_{i\cdot}) = f(\mathcal{R}_{i1}|Z_{i1}, W_{i\cdot})$.

In *Assumption 2*, we allow Z_{i1} to be MNAR such that its missingness depends on the true value of Z_{i1} but does not depend on the other variables with missing values. For addressing more general missingness mechanisms, see **Supplementary Section A**.

2.2 Imputation and importance sampling

Let $Z_{i,mis}$ and $Z_{i,obs}$ denote the missing and observed elements of $Z_{i\cdot}$, respectively. Under a full joint model for the variables with missingness, we can impute missing values of $Z_{i\cdot}$ from $f(Z_{i,mis}|Z_{i,obs}, \mathcal{R}_{i\cdot} = R_{i\cdot})$. In practice, we often approximate a draw from the full joint distribution by iteratively drawing missing values for each variable in Z from its full conditional distribution, $f(Z_{ij}|Z_{i,-j}, \mathcal{R}_{i\cdot} = R_{i\cdot})$. Then, we repeat this iterative process many times to obtain M imputed datasets. Rather than specifying the full joint model for all variables with missingness, a chained equations strategy involves directly specifying a model for each full conditional distribution, $f(Z_{ij}|Z_{i,-j}, \mathcal{R}_{i\cdot} = R_{i\cdot})$.[4] It can be challenging in general to determine how to specify these conditional models as a function of $R_{i\cdot}$. Under *Assumptions 1-2*, however, these imputation distributions can be simplified.

First, we consider imputation for Z_{ij} in $Z_{i2}, \ldots, Z_{ik}$. Under *Assumptions 1-2*, $f(Z_{ij}|Z_{i,-j}, \mathcal{R}_{i\cdot} = R_{i\cdot}) = f(Z_{ij}|Z_{i,-j}, \mathcal{R}_{ij} = 1) = f(Z_{ij}|Z_{i,-j})$. This is the same distribution we would use to impute Z_{ij} under standard MAR assumptions, and we can apply our usual strategies for performing this imputation, e.g. by approximating $f(Z_{ij}|Z_{i,-j})$ with a regression model.

Now, we consider the imputation distribution for Z_{i1}. Under *Assumption 1*, we can impute missing Z_{i1} from

$$f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i\cdot} = R_{i\cdot}) = f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 0)$$

Parameters from this distribution are not identified from the observed data without additional assumptions. However, we note that

$$f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 0) = \frac{P(\mathcal{R}_{i1} = 0|Z_i)}{P(\mathcal{R}_{i1} = 0|Z_{i,-1})} f(Z_{i1}|Z_{i,-1}) = \frac{P(\mathcal{R}_{i1} = 0|Z_i)}{P(\mathcal{R}_{i1} = 0|Z_{i,-1})} \left[\sum_r f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = r) P(\mathcal{R}_{i1} = r|Z_{i,-1}) \right]$$

$$= P(\mathcal{R}_{i1} = 0|Z_i) \left[f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 1) \frac{P(\mathcal{R}_{i1} = 1|Z_{i,-1})}{P(\mathcal{R}_{i1} = 0|Z_{i,-1})} + f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 0) \right]$$

The term $f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 0)$ appears on both the left and the right of this expression. Rearranging this expression and using that $P(\mathcal{R}_{i1} = 0|Z_{i\cdot}) = P(\mathcal{R}_{i1} = 0|Z_{i1}, W_{i\cdot})$, we have that

$$f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 0) \propto \frac{P(\mathcal{R}_{i1} = 0|Z_{i1}, W_{i\cdot})}{1 - P(\mathcal{R}_{i1} = 0|Z_{i1}, W_{i\cdot})} f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 1) \qquad (Eq.\ 1)$$

Unlike $f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 0)$, there is information in the data to estimate parameters in distribution $f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 1)$. The term $P(\mathcal{R}_{i1} = 0|Z_{i1}, W_{i\cdot})$ is not identified from the observed data, and we will need to make untestable assumptions about this distribution. We will address this challenge later on. Even if this missingness probability were known, drawing from *Eq. 1* can still be difficult, since the distribution may only be known up to proportionality in some cases. Rejection sampling and other statistical techniques can be applied to draw from *Eq. 1* directly, but these approaches can be computationally expensive and require custom software.

One option is to approximate a draw from *Eq. 1* using importance sampling as in Tanner (1993) and Little and Rubin (2002).[12,4] Define functions $j(z) = f(z|Z_{i,-1}, \mathcal{R}_{i1} = 1)$ and $h(z) = f(z|Z_{i,-1}, \mathcal{R}_{i1} = 0)$. We can approximate a draw from $h(z)$ by drawing multiple candidate imputations $z^1, \ldots, z^M$ from $j(z)$. Then, we select candidate draw z^m with probability proportional to $h(z^m)/j(z^m)$ to obtain a *single* imputation of Z_{i1}. This process can then be repeated multiple times to obtain multiple imputations. This importance sampling method can be applied if

1. The support of $j(z)$ contains the support for $h(z)$.

2. Function $h(z)/j(z)$ is bounded.

The first requirement may often be met for $j(z)$ and $h(z)$ as defined above. However, many candidate draws may be needed when $j(z)$ and $h(z)$ are very different, i.e. the distribution of observed Z_{i1} is very different than the distribution of missing Z_{i1}. The second requirement is satisfied if $w(z) = \frac{P(\mathcal{R}_{i1}=0|z,W_{i\cdot})}{P(\mathcal{R}_{i1}=1|z,W_{i\cdot})}$ is bounded in z. $w(z)$ will, of course, be bounded below by 0. However, additional assumptions are needed to ensure $w(z)$ is bounded above. We can ensure that $w(z)$ is bounded above if we assume there is some (possibly small) probability ϵ such that $\epsilon < P(\mathcal{R}_{i1} = 1|z, W_{i\cdot})$ for all z. In other words, the probability of observing Z_{i1} must always be non-zero. While this may not strictly hold for some Z_{i1} (e.g. those defined on the real line under

logistic regression), we may still reasonably apply this importance sampling strategy if the probability of drawing very extreme candidates for Z_{i1} is small.

The above approach can become computationally expensive, since we need many candidate draws from $j(z)$ in order to obtain a single imputed value from $h(z)$. An alternative approach is to first obtain M multiple imputations of Z_{i1} and to weight these multiple imputations proportional to $w(z)$ in the data analysis. The exact way in which these weights should be carried through in the analysis of multiply imputed data, however, is not obvious. Previously, Carpenter et al. (2007) proposed a strategy for incorporating such weights into analysis of multiply imputed $Z_{.1}$ as described in **Section 2.3** below.[7] In this paper, we will propose a different strategy to incorporate such weights into data analysis that maintains the simplicity of the method in Carpenter et al. (2007) but gives better properties in terms of bias in estimating parameters of interest.[7]

2.3 Weighting strategy of Carpenter et al. (2007)

Suppose we obtain multiple imputations of missing values in Z_{i1} *as if missingness were MAR* from $f(Z_{i1}|Z_{i,-1}, \mathcal{R}_{i1} = 1)$. Let θ denote our parameter of interest. A common strategy for obtaining the final estimate of θ for multiply imputed data is to take the average of parameter estimates obtained for each of the individual imputations, here denoted $\hat{\theta}_1, \ldots, \hat{\theta}_M$. To account for the MNAR missingness, Carpenter et al. (2007) proposes taking a *weighted average* of these estimates.[7] The structure of the weight proposed by Carpenter et al. (2007) was motivated by the relation in *Eq. 1*, in the special case where the missingness model for Z_{i1} can be approximated by the following logistic regression: $\text{logit}\left(P(\mathcal{R}_{i1} = 1|Z_{i1}, W_{i.})\right) = \phi_0 + \phi_1 Z_{i1} + \phi_W^T W_{i.}$. Omitting some details, the weight for imputation m proposed in Carpenter et al. (2007) is defined as

$$\alpha_m \propto \exp\left(-\phi_1 \sum_{i:R_{i1}=0}^{n} Z_{i1m}\right) \qquad (Eq.\ 2)$$

where the α's are rescaled so that $\sum_{k=1}^{M} \alpha_k = 1$ and Z_{i1m} denotes the m^{th} imputation of Z_{i1}. Point estimates and standard errors under MNAR are then obtained as follows:

$$\hat{\theta}_{MNAR} = \sum_{m=1}^{M} \alpha_m \hat{\theta}_m \qquad (Eq.\ 3)$$

$$Var(\hat{\theta}_{MNAR}) = \sum_{m=1}^{M} \alpha_m Var(\hat{\theta}_m) + (1 + 1/M) \sum_{m=1}^{M} \alpha_m \left[\hat{\theta}_m - \hat{\theta}_{MNAR}\right]^2$$

In this analysis, ϕ_1 is treated as a sensitivity parameter, and the final analysis is performed multiple times across a plausible range of ϕ_1 values. This analysis approach is easy to implement and allows the imputation to be separated from the handling of MNAR missingness. Unlike more commonly-used MNAR sensitivity analysis strategies such as those in Tompsett et al. (2018), this approach does not require $Z_{.1}$ to be imputed separately for each fixed value of the sensitivity parameter.[5]

As discussed in Carpenter et al. (2013), however, this approach requires the true θ value to be within the range of the $\hat{\theta}_j$ estimates obtained from each of the imputed datasets under MAR.[13] Rezvan et al. (2015) demonstrates that the approach in Carpenter et al. (2007) can produce substantial bias when this assumption is not met.[7,8] Additionally, Rezvan et al. (2015) shows that this approach does not guarantee a consistent estimate of θ even when this assumption is met.[8] Smuk (2015) provides a correction to these weights that may reduce this bias in some cases, but this correction can only be applied when we have MNAR missingness in a single, normally-distributed variable.[9] Additionally, the method in Smuk (2015) cannot provide consistent parameter estimates when the true value of θ is outside the range of estimates obtained under MAR assumptions.

2.4 Proposed weighting and analysis strategy

The importance sampling logic in **Section 2.2** implies that each imputed value of Z_{i1} should be weighted proportional to $\frac{P(\mathcal{R}_{i1}=0|Z_{i1},W_{i.})}{1-P(\mathcal{R}_{i1}=0|Z_{i1},W_{i.})}$, where weights are rescaled to sum to 1 *for each subject*. Instead, the Carpenter et al. (2007) approach weights vector $Z_{.1}$ by the *product* of the unscaled weights for each individual Z_{i1}, and the resulting aggregate weights are scaled to sum to 1 across imputations.[7] This approach no longer distinguishes between "good" and "bad" imputations of individual Z_{i1} (in terms of their corresponding weights relative to the target distribution under MNAR) and instead considers imputed datasets in aggregate. We posit that this weight aggregation step is the primary source of residual downstream bias in the final analysis.

To address this issue, we propose maintaining separate weights at the individual level and instead performing our analysis using imputation stacking. The idea behind imputation stacking is that multiply imputed datasets are stacked on top of each other

to form a large, Mn by p matrix. θ can then be estimated by performing our target analysis on the stacked dataset. Previous work has shown that this approach can produce estimates of θ equivalent to analysis by Rubin's combining rules.[14] Historically, this imputation stacking approach has been difficult to implement owing to the lack of easy-to-use estimators for corresponding standard errors. Wood et al. (2008) proposed a simple method for estimating standard errors for stacked data analysis, but we showed that this approach can result in substantially biased standard error estimates in many settings.[15,10] Recently, Beesley and Taylor (2020) proposed a new strategy for estimating valid standard errors based on the observed data information principle of Louis (1982).[10,16] An alternative bootstrap-based estimator has also been proposed in Bernhardt (2019).[11] These advancements have made the stacked imputation strategy an accessible and appealing analysis framework.

We propose handling MNAR missingness in Z_{i1} through a weighted analysis of the stacked data as follows. This approach is summarized in **Figure 1**.

• **Step 1:** Obtain M multiple imputations of Z assuming ignorable missingness (MAR).

Obtain M multiple imputations of the missing data using chained equations imputation, where each variable Z_{ij} with missingness is imputed from a regression model approximation to $f(Z_{ij}|Z_{i,-j}, \mathcal{R}_{ij} = 1)$, denoted $\tilde{f}$. Following logic commonly-used in chained equations imputation, we approximate a draw from this distribution by first drawing the corresponding parameter, which we will denote β_j, as follows:

$$\begin{aligned} &\text{Draw parameter } \beta_j \text{ from } \tilde{f}(\beta_j|Z^{imp}_{.,-j}, Z^{obs}_{.j}, \mathcal{R}_{.j} = 1) \\ &\text{Impute missing } Z_{ij} \text{ from } \tilde{f}(Z_{ij}|Z_{i,-j}, \mathcal{R}_{ij} = 1; \beta_j) \end{aligned} \quad (Eq.\ 4)$$

where $Z^{imp}_{.,-j}$ denotes the most recent imputed version of variable $Z_{.,-j}$ and $Z^{obs}_{.j}$ denotes the fully-observed elements in $Z_{.j}$. In practice, we can obtain a draw of β_j from a multivariate normal distribution with mean and covariance matrix estimated from fitting a model for $Z_{.j}|Z_{.,-j}$ to the subset of recently imputed data *for which* $Z_{.j}$ *is observed*. Alternatively, β_j could be obtained by fitting a model to a bootstrap sample of the same subset of the imputed data. The key here is that parameters used for imputing $Z_{.1}$ are drawn only using data $Z_{i.}$ from subjects i with *observed* Z_{i1}, since the distribution of $Z_{i1}|Z_{i,-1}$ conditioning on $R_{i1} = 1$ is not the same as the unconditional distribution. Fortunately, this approach for obtaining parameter draws is used by many commonly-used statistical packages to impute missing data under MAR assumptions, e.g. package *mice* in R and *PROC MI* in SAS. Therefore, we can often impute Z using standard imputation software assuming ignorable missingness.

• **Step 2:** Stack multiple imputations

Generate a Mn by p dataset by stacking the M multiple imputations on top of each other, where complete cases are also repeated M times. An alternative formulation where complete cases are included only once is discussed in Beesley and Taylor (2020).[10]

• **Step 3:** Calculate weights

Let Z_{i1m} denote the m^{th} multiple imputation of Z_{i1}. We then define weights

$$\omega_{im} \propto \frac{P(\mathcal{R}_{i1} = 0|Z_{i1m}, W_{i.})}{1 - P(\mathcal{R}_{i1} = 0|Z_{i1m}, W_{i.})} \quad (Eq.\ 5)$$

that are rescaled such that $\sum_{k=1}^{M} \omega_{ik} = 1$. We augment each row of the stacked dataset with the corresponding weight, where rows corresponding to subjects with observed Z_{i1} are assigned weight $1/M$.

• **Step 4:** Estimate parameter of interest

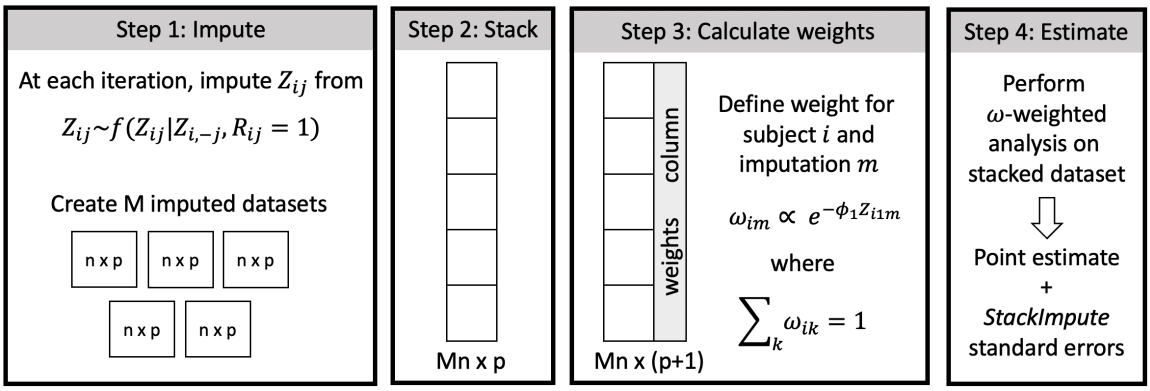
Let θ be our parameter of interest. Estimate $\hat{\theta}$ by performing a *weighted* version of our target analysis on the stacked dataset, where weights are defined as in Step 3. For example, if our goal is to estimate the mean of $Z_{.1}$, we can estimate a weighted mean from the stacked dataset. If all models are correctly specified, this will produce a valid estimate for θ. We can estimate corresponding standard errors using the strategies in **Section 3**. We provide software for applying these standard error estimators in R package *StackImpute*.

2.5 Modeling missingness

The structure of the weights in *Eq. 5* depends on an assumed model for whether or not Z_{i1} is observed, and a key limitation of this approach is that this missingness relationship may often be unknown. Suppose, however, that we posit a *working* regression model structure for this missingness model as follows:

$$g\left(P(\mathcal{R}_{i1} = 1|Z_{i1}, W_{i.})\right) = \phi_0 + \phi_1 Z_{i1} + \phi_2^T W_{i.} \quad (Eq.\ 6)$$

Figure 1 Visualization of proposed imputation and stacked data analysis procedure [1]



[1] ϕ_1 is a sensitivity analysis parameter. Steps 3-4 can be repeated for multiple values of ϕ_1. R package *StackImpute* (available at https://github.com/lbeesleyBIOSTAT/StackImpute) can be used to estimate standard errors via the methods in **Section 3**.

where ϕ_2 may be a vector. Then, we can define

$$\omega_{im} \propto \frac{1 - g^{-1}\left(\phi_0 + \phi_1 Z_{i1m} + \phi_2^T W_{i.}\right)}{g^{-1}\left(\phi_0 + \phi_1 Z_{i1m} + \phi_2^T W_{i.}\right)}. \quad (Eq.\ 7)$$

In general, this weight will not have a nice form, and it depends on unknown parameters ϕ_0, ϕ_1, and ϕ_2. Generally, ϕ_1 will not be identifiable from the observed data, and we will instead treat it as a fixed sensitivity parameter. Strategies guiding the choice of ϕ_1 are discussed in **Section 2.6**. For a fixed value of ϕ_1, parameters ϕ_0 and ϕ_2 can be estimated by fitting the model in *Eq. 6* with fixed offset $\phi_1 Z_{i1m}$ to the (unweighted) dataset obtained by stacking the multiple imputations. This can be repeated to generate weights for different fixed values of ϕ_1 within a plausible window. Unlike usual sensitivity analysis strategies applied within the chained equations algorithm as in Tompsett et al. (2018), this sensitivity parameter can be directly interpreted as the variable's association with its own missingness, adjusting for $W_{i.}$.[5]

One downside of this strategy is that it requires us to specify the functional relationship between missingness in $Z_{.1}$ and fully-observed variables, W. In the special case where *Eq. 6* corresponds to a logistic regression, however, the structure of the weights simplifies as follows:

$$\omega_{im} \propto \exp\left(-\phi_1 Z_{i1m}\right) \quad (Eq.\ 8)$$

The contribution of W drops out of these weights after we rescale the weights such that $\sum_{k=1}^{M} \omega_{im} = 1$. In other words, the weights become a simple function of (1) the multiple imputations of Z_{i1} and (2) the fixed sensitivity parameter, ϕ_1. This result holds true for a more general class of logistic regression missingness models where W is allowed to have more complicated relationships with $\mathcal{R}_{.1}$, including non-linear effects or interactions between variables in W.

2.6 Choosing values for the sensitivity parameter

Even in settings where the degree of MNAR adjustment is entirely captured by ϕ_1 as in *Eq. 8*, choosing values for ϕ_1 is not straightforward. However, we can leverage existing statistical tools for eliciting sensitivity analysis parameters to guide our choice of ϕ_1. Several strategies are summarized here and discussed in more detail in **Supplementary Section B**.

One common strategy called "tipping point" analysis involves estimating θ across a wide interval of sensitivity parameters.[5,17] Then, we identify bounds on the sensitivity parameter for which our study conclusions are changed in a meaningful way. Our level of concern about deviations from MAR is then converted into a question of the plausibility of these bounds.

Since ϕ_1 is defined in terms of the W-adjusted association between $Z_{.1}$ and $\mathcal{R}_{.1}$, it can still be difficult to determine whether a single fixed value of the sensitivity parameter is scientifically plausible. One solution discussed in Tompsett et al. (2020)[18] is to reformulate the problem in terms of more easily interpretable sensitivity parameters. Using a single set of multiple imputations obtained under MAR, we can repeat our stacked data analysis across multiple values of ϕ_1 to characterize how values of ϕ_1 are related to the target parameter, θ. For each chosen value for ϕ_1, we can also use stacked and weighted analysis to estimate an easier-to-interpret parameter related to missingness (e.g. $P(\mathcal{R}_{.1} = 1|Z_{i1})$), denoted π_1. We can then evaluate our sensitivity

analysis results in terms of the relationship between θ and π_1 rather than ϕ_1.

Subject matter experts can also help choose reasonable values for ϕ_1 or some transformation, π_1. In Tompsett et al. (2020)[18] and Rezvan et al. (2018)[19], multiple subject matter experts were asked to provide their intuition regarding expected differences between subjects with missing and observed data. These expectations were then combined using a process called linear pooling to obtain a distribution of expert-elicited values for the sensitivity parameter. While previously applied to pattern mixture model-based sensitivity analysis, this approach can also be applied under our selection modeling framework, where expert-elicited summary statistics can be used to inform choices for ϕ_1 either directly or through some intermediate sensitivity parameter, π_1.

3 Variance estimation strategies

In Beesley and Taylor (2020), we proposed a strategy for estimating standard errors for $\hat{\theta}$ obtained using maximum likelihood estimation based on stacked and weighted data as follows.[10] Let J_{com} be the negative of the second derivative matrix of the complete data log-likelihood function for the target analysis, and let U_{com} be the first derivative matrix of the complete data log-likelihood function. Let $J^i_{com}(\theta)$ and $U^i_{com}(\theta)$ be the contributions to the complete data information matrix and score matrix for subject i respectively. We approximate

$$I_{obs}(\theta) \approx \sum_i \sum_m \omega_{im} J^i_{com}(Z_{i.m};\theta) - \sum_i \sum_m \omega_{im} \left[U^i_{com}(Z_{i.m};\theta) - \bar{U}^i_{com}(Z_{i..};\theta)\right]^{\otimes 2} \quad (Eq.\ 9)$$

where $\bar{U}^i_{com}(Z_{i..};\theta) = \sum_k \omega_{ik} U^i_{com}(Z_{i.k};\theta)$. We can evaluate this expression at the maximum likelihood estimator for θ, $\hat{\theta}$, obtained from maximizing the complete data log-likelihood using the weighted, stacked dataset. Inverting the resulting matrix $I_{obs}(\hat{\theta})$ will provide an estimate for the observed data covariance matrix for $\hat{\theta}$.

A limitation of the estimator in *Eq. 9* is that it requires us to obtain the complete data score and information matrices and can only be applied when our target analysis is maximum likelihood estimation with a valid log-likelihood function. Additionally, this approach can produce inaccurate or even negative variances when n is small (e.g., n = 100). An alternative method proposed in Bernhardt (2019) uses bootstrap methods to account for so-called "between imputation" variation as follows.[11] Let V_{stack} be the estimated covariance matrix output by the stacked and weighted analysis, obtained using standard error estimation strategies that account for the weights. For example, for a generalized linear model with a dispersion parameter, the dispersion parameter must also be estimated using weighted residuals. The matrix V_{stack} represents the "within imputation" variation. To capture the "between imputation" variation, we estimate θ on many bootstrap replicates of the stacked data. Unlike standard bootstrap replication, we obtain each bootstrap replicate of the stacked data by drawing with replacement from the set of indices $\{1, \ldots, M\}$ corresponding to the M imputed datasets and then construct the bootstrapped stacked dataset composed of the drawn M imputed datasets, where individual imputed datasets may appear in the stack multiple times. We then re-scale weights ω_{im} in the bootstrapped stack so that the weights again sum to 1 within individuals. Let $V_{between}$ be the estimated covariance matrix of the resulting $\hat{\theta}$ estimates across bootstrap samples of the imputed datasets. We then estimate the overall covariance matrix as follows:

$$Var(\hat{\theta}_{MNAR}) = V_{stack} + (1 + M)\, V_{between} \quad (Eq.\ 10)$$

One unappealing feature of the bootstrap-based estimator for $V_{between}$ proposed in Bernhardt (2019) is that it may require a large number of bootstrap samples, which can result in slow estimation.[11] Instead, we propose estimating the "between imputation" variation using a jackknife estimator, defined with respect to leave-one-out *imputations*. We estimate $V_{between}$ as

$$V_{between} = \frac{M-1}{M} \sum_m \left[\hat{\theta}^{(m)} - \bar{\theta}\right]^{\otimes 2} \qquad \bar{\theta} = \frac{1}{M} \sum_m \hat{\theta}^{(m)}$$

where $\hat{\theta}^{(m)}$ is estimated by fitting the model on the stacked data excluding the m^{th} multiple imputation, again re-scaling the weights to sum to 1 within subjects.

4 Simulations reproducing Rezvan et al. (2015): MNAR outcome missingness

Rezvan et al. (2015) conducted a simulation study to demonstrate settings in which the method from Carpenter et al. (2007) does and does not perform well.[8,7] Here, we reproduce this simulation study and compare the results obtained using our proposed method to complete case analysis and the method in Carpenter et al. (2007).

4.1 Simulation set-up

Suppose our goal is to estimate the association between outcome variable Z_1 (partially missing) and covariate Z_2 (fully-observed), and suppose we have MNAR missingness in outcome Z_1 dependent on the true value of Z_1 and Z_2. For each of several simulation settings, we generate 1000 simulated datasets of n = 100 or 1000 subjects. In all settings, we generate $Z_2 \sim N(0,1)$. We then generate Z_1 using one of two models: (1) $Z_1 \sim N(0.5Z_2, 1)$ or (2) $\text{logit}(P(Z_1 = 1|Z_2)) = 0.5Z_2$. In both settings, we then impose roughly 50% missingness in Z_1 using the following logistic regression model: $\text{logit}(P(Z_1 \text{ observed } |Z)) = \phi_1 Z_1 + Z_2$ where $\phi_1 = 1, 0.5$, or 0. We then obtain M multiple imputation of the missing values of Z_1 under MAR assumptions, where M takes values 5, 10, 50, 100, 500, or 1000. We apply the proposed method and the method in Carpenter et al. (2007) to estimate parameters in the outcome model (either linear or logistic regression for $Z_1|Z_2$).[7] We obtain parameter estimates under different *assumed* values for ϕ_1, including 0, 0.2, 0.5, 0.8, 1, and 1.2.

4.2 Point estimation

Figure 2a shows the average estimated values for outcome model parameters across 1000 simulated datasets, assuming ϕ_1 is known to equal 1. Complete case analysis and analysis of imputations obtained under MAR (not shown, similar to complete case estimates) produced substantial bias in estimating outcome model parameters. Although it results in reduced bias compared to complete case analysis, the method in Carpenter et al. (2007) produced substantial residual bias even when n and M were large.[7] In contrast, the proposed method had small or negligible bias in estimating all model parameters as long as M, the number of multiple imputations, was large enough (e.g. $\geq$ 50). For example, the method in Carpenter et al. (2007) resulted in biases in the linear regression coefficient of Z_2 up to 21% for n=100 and up to 14% for n=1000 with $M = 1000$. In comparison, the proposed method gave much smaller biases, with corresponding biases in the linear regression coefficient of Z_2 down to 9% for n=100 and down to 2% for n=1000. Results were similar for $\phi_1 = 0.5$. In **Section D**, we describe a second simulation study in which missingness was generated for multiple covariates, one of which was MNAR. Results were similar. Additional simulations addressing multiple variable and more complicated MNAR missingness are presented in **Section E**. In these simulations, the extensions of the proposed method described in **Section A** resulted in little bias in estimating outcome model parameters for well-specified sensitivity parameters.

We also compare the performance of the proposed method in terms of point estimation with two existing MNAR-handling strategies within the chained equations literature in **Table C.1**. We implement the method in Tompsett et al. (2018) using the best possible value for the corresponding offset parameter related to $R_{.1}$, which was estimated by fitting the pattern mixture model in the true simulated data.[5] The method in Jolani (2012) implemented in *mice.impute.ri* was also applied.[6] We found that the method in Jolani (2012) produced substantial residual bias in estimating outcome model parameters. The method in Tompsett et al. (2018) produced little bias when the corresponding offset sensitivity parameter was correctly specified. We observed similar results when these methods were applied to multiple variable missingness in **Table D.1**.

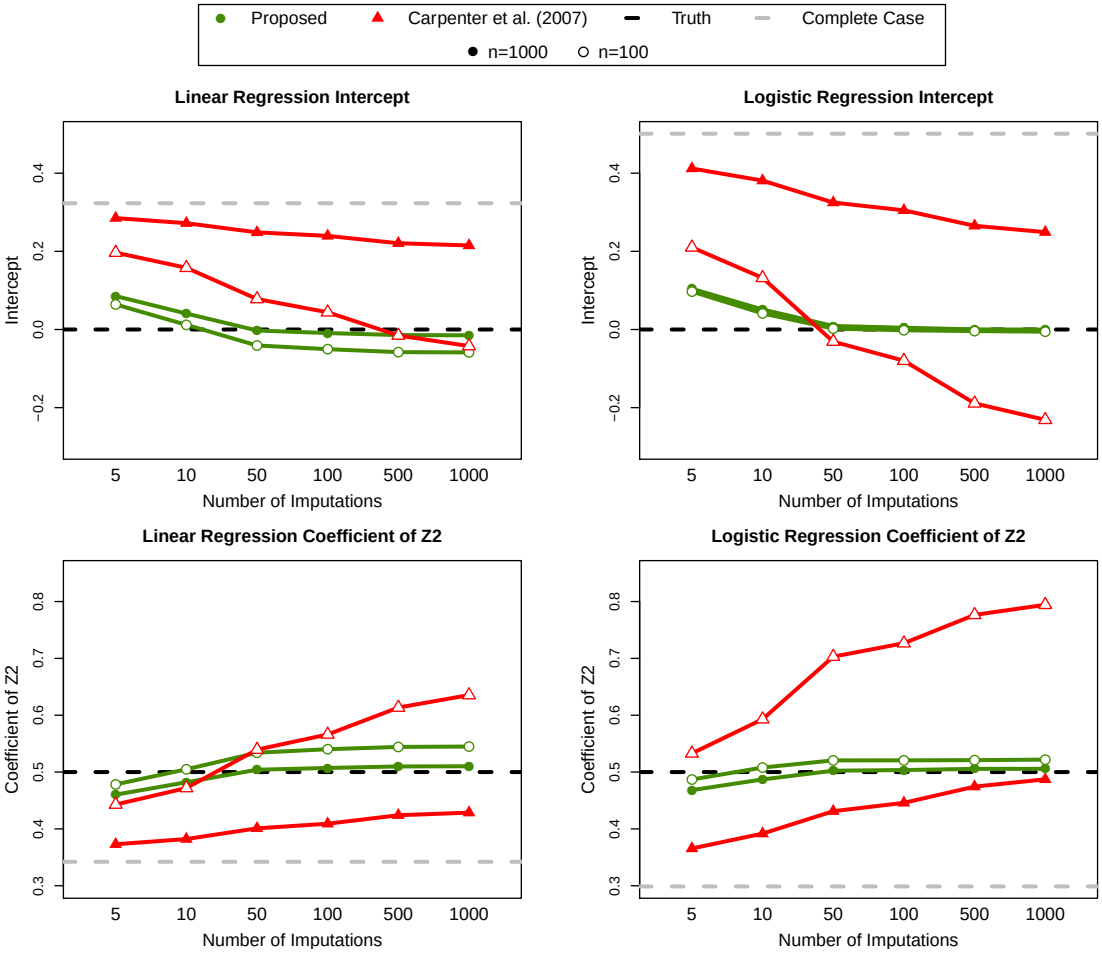
As discussed in **Section 2.6**, we will rarely know the true value of ϕ_1 or any sensitivity parameter. We can apply these methods across different *assumed* values for ϕ_1 as a sensitivity analysis to departures from MAR. Results are shown in **Figure 2b**. Point estimates from the method in Carpenter et al. (2007) did not vary much across assumed ϕ_1 values above about 0.5.[7] As demonstrated in **Figure C.1**, this is because the true value of the outcome model parameter is outside the range of estimates obtained from MAR-based imputation (range between 0.32 and 0.45, mean = 0.39). In **Figure C.2**, we compare the imputation-specific weights obtained for the method in Carpenter et al. (2007) and for our proposed method using the data visualization proposed in Heraud-Bousquet et al. (2012).[20] The final weighted estimate for the Carpenter et al. (2007) method is dominated by the imputed dataset producing the most extreme MAR-based estimates for larger values of $|\phi_1|$, with weights near 1 for a single imputed dataset.[7] In contrast, the proposed method defines weights at the subject level, and the largest imputation-specific weight obtained for *any* subject was near 0.5. For most subjects, the largest weight was about 0.06. These smaller imputation- and subject-specific weights produce a much more stable estimation of model parameters that is much less sensitive to extreme imputations drawn for individual subjects.

4.3 Estimation of standard errors

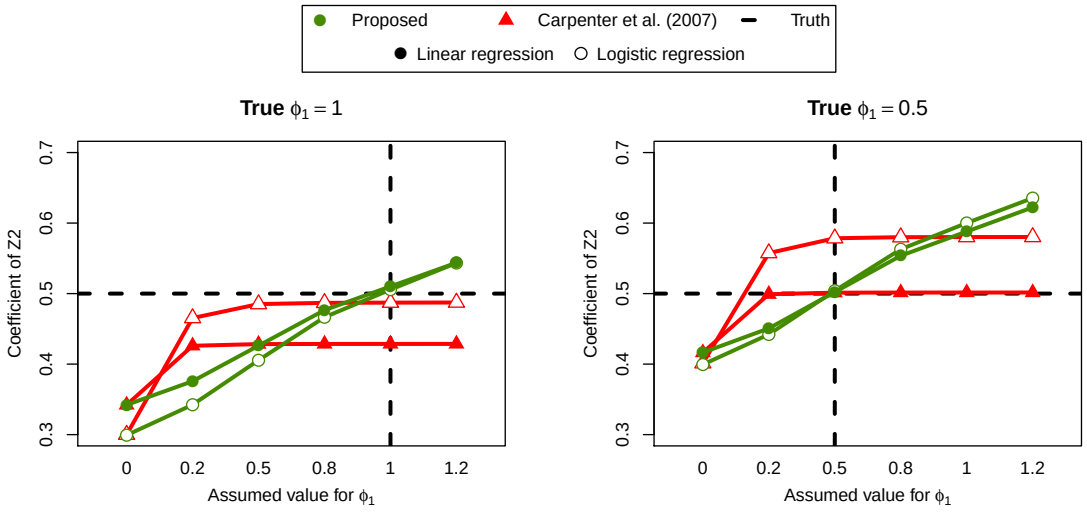
We may also be interested in estimating standard errors for regression model parameters. We apply the methods in **Section 3** to estimate standard errors for the proposed stacked and weighted analysis method assuming that ϕ_1 is correctly specified. We calculate corresponding 95% confidence intervals for estimating the coefficient of Z_2 in linear or logistic regression models

Figure 2 Average estimated outcome model parameters across 1000 simulated datasets under MNAR missingness in outcome Z_1.

(a) Estimates assuming true ϕ_1 is known (results shown for true $\phi_1 = 1$)



(b) Estimates across assumed values for ϕ_1. Results shown true $\phi_1 = 1$ (left) and 0.5 (right)[1]



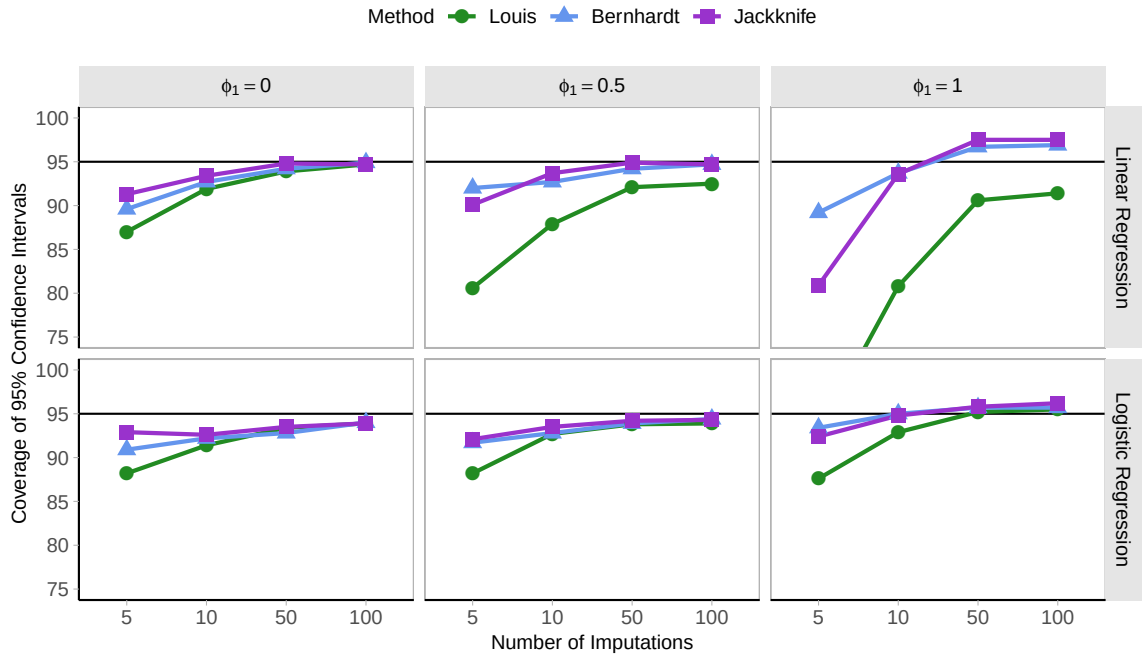
[1] Results shown for $M = 1000$ and $n = 1000$.

using each of the three variance estimation strategies and assuming a normal distribution approximation (point estimate ± 1.96 × standard error estimate). Results are shown in **Figure 3**. When the target model was logistic regression, all of the variance estimation strategies produced similarly good coverage rates as long as M was large enough (e.g., >50). However, the story is more complicated for coverage rates when the target outcome model is linear regression. When true ϕ_1 was moderate or small (e.g., $\phi_1 \leq 0.5$), the method proposed in Bernhardt (2019) and our jackknife modification produced nominal coverage for large M.[11] However, these two approaches resulted in slight over-coverage when ϕ_1 was large (e.g. 1). The method in *Eq. 9* based on the observed data information principle in Louis (1982) resulted in small under-coverage for all values of $\phi_1 \neq 0$, with stronger under-coverage seen for larger ϕ_1.[16]

As noted in Rezvan et al. (2015), the distribution actually used to impute normally-distributed $Z_{.1}$ within the chained equations imputation algorithm has heavier tails than the "ideal" normal distribution when the corresponding dispersion parameter is not known.[8] To evaluate whether this explains the observed over- and under-coverages, we repeated these simulations after imputing Z_1 from a normal distribution with dispersion parameter fixed at the simulation truth. This modified imputation strategy did not impact the resulting coverage rates (results not shown), indicating that this slight over- and under-coverage was not driven by the heavy-tailed imputation. Similar results were seen in simulations with multiple covariates as discussed in **Section D**.

Figure C.3 provides the average run-time for each of these variance estimation strategies under a normally-distributed imputed outcome with $n = 1000$. At $M = 100$, the method in *Eq. 9* took on average only 1.4 seconds to estimate standard errors. In comparison, the method from Bernhardt (2019) and our jackknife modification took an average of roughly 39 and 25 seconds, respectively.[11] While this difference will be negligible for many analyses, the shorter runtime of the method in *Eq. 9* may produce a much shorter aggregate runtime when sensitivity analyses are performed across a large grid of ϕ_1 values. The comparison between runtime for the proposed analysis and standard pattern mixture-type imputation will vary based on the number of sensitivity parameter evaluations, the number of multiple imputations, and the complexity of the multiple imputation procedure.

Figure 3 Coverage of 95% confidence intervals for the coefficient of Z_2 from stacked and weighted analysis across 1000 simulated datasets assuming true ϕ_1 is known



5 Illustrative example: missingness of HPV status in patients with oropharyngeal cancer

We apply the proposed methods to address potential MNAR missingness in a study of N=840 patients newly-diagnosed with oropharyngeal squamous cell carcinoma at the University of Michigan. Baseline characteristics including smoking status, age,

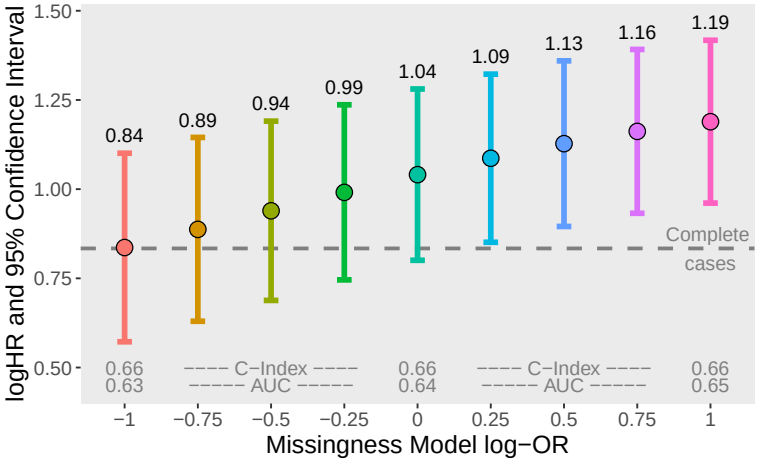
cancer stage, and comorbidities were collected at the time of study enrollment (at or soon after diagnosis), and patients were then followed for cancer-related outcomes including overall survival. For over 30% of patients, HPV (human papillomavirus) status was not evaluated at baseline. Baseline comorbidities status (none/mild/moderate/severe) is missing for roughly 27% of patients, and there is a very small amount of missingness in smoking status and cancer stage. For additional details about patient recruitment, data collection, and study descriptives, we refer the reader to Beesley et al. (2019).[21]

Suppose our interest lies in modeling overall survival as a function of baseline characteristics. For the baseline covariates of interest, only 45% of patients have complete data. To improve estimation efficiency and guard against bias from complete case analysis, we want to perform multiple imputation to handle the missing data. However, we have concerns about the reasonableness of the MAR assumption. In particular, we consider missingness in HPV status. Missingness in HPV status is clearly related to year of enrollment for this cohort, reflecting the increasing acceptance of HPV status as a key prognostic factor for oropharyngeal cancer patients (**Figure F.1**). As shown in **Table F.1**, missingness in HPV status is also associated with smoking status even after adjusting for year of enrollment, with current smokers being less likely to have HPV status available relative to never smokers (log-odds ratio -0.13, 95% CI: -0.21, -0.04). In terms of oropharyngeal cancer etiology, this makes sense; two strong risk factors for oropharynx cancer development are smoking and HPV positivity. If the patient was a current smoker, doctors may have been less inclined to recommend testing for HPV status (at least, for earlier enrollment periods before HPV testing had become a standard part of patient care). However, additional unobserved factors such as sexual history could have also informed decision-making for whether a patient was tested for HPV infection. This could induce a MNAR association between HPV testing and true HPV status, where untested people may be less likely to be positive even after adjusting for other observed baseline variables and calendar time of enrollment. We are interested in exploring to what extent our estimated parameters in a model for overall survival are impacted by our assumptions regarding HPV missingness. In our analysis, we will allow HPV missingness to depend on true HPV status given covariates, but we will assume that HPV status missingness does not depend on any other unobserved information. **Table F.1** suggests there may also be an association between missingness and comorbidities, which is missing for 27% of patients. If this association is not induced by the association between comorbidities and HPV status, our working missingness model may only partially capture the MNAR dependence.

We applied the method in **Figure 1** as follows. First, we obtained 50 multiply imputed datasets assuming HPV missingness is MAR. Missingness for other baseline covariates was also assumed to be MAR. Details on this imputation procedure can be found in **Supplementary Section F**. We then obtained a stacked dataset and weighted the dataset proportional to $\exp\left(-\phi_1 \mathcal{I}[\text{HPV positive}]\right)$, where ϕ_1 corresponds to the log-odds ratio for *observing* HPV status for HPV positive vs. HPV negative patients. We fit a weighted Cox proportional hazards regression model for overall survival using this stacked data, where ϕ_1 was varied between -1 and 1. Relative to estimated log-odds ratios for missingness (**Table F.1**), a value of $|\phi_1| > 0.2$ represents very extreme MNAR dependence. The Cox proportional hazards model adjusted for HPV status, smoking status, ACE27 comorbidities, overall cancer stage, and age at cancer diagnosis. We applied the method in *Eq. 9* to estimate corresponding standard errors using the partial log-likelihood.

Figure 4 shows the estimated log-hazard ratio for HPV positivity in the overall survival regression model as a function of ϕ_1. We see that the point estimate for the log-hazard ratio does change in magnitude across ϕ_1. For example, the log-hazard ratio is estimated as 1.19 (95% CI: 0.96, 1.42) for $\phi_1 = 1$ and 0.84 (95% CI: 0.57, 1.10) for $\phi_1 = -1$. However, for more reasonable values of $|\phi_1|$ consistent with observed associations between missingness and other variables (**Table F.1**), the log-hazard ratio only varies between about 0.99 and 1.09. Additionally, the 95% confidence intervals across all ϕ_1 are still far from 0 even for more extreme values of ϕ_1. If our goal was to assess whether HPV status was associated with overall survival for patients newly-diagnosed with oropharyngeal cancer, our study findings would not be strongly impacted by assuming MAR. In this example, we may be more concerned about the magnitude of the association between HPV status and overall survival if we are wanting to use the resulting model to predict likely survival outcomes for new patients. To compare the impact of the choice of ϕ_1 on discrimination of resulting 5-year overall survival estimates, we calculated 5-year survival predictions for each of the 378 patients with complete covariate data using each of the estimated survival models. We report the corresponding C-Indices and area under the receiver operating curve (AUC) in **Figure 4**. The estimated C-Indices and AUC did not vary much across different values of ϕ_1.

Figure 4 Estimated associations between HPV status and overall survival across assumed values for ϕ_1 [1]



[1] HR denotes hazard ratio, OR denotes odds ratio. For each value of ϕ_1, point estimates come from a weighted Cox proportional model for overall survival adjusting for HPV status, smoking status, ACE27 comorbidities, overall cancer stage, and age at cancer diagnosis. The scenario with $\phi_1 = 0$ corresponds to analysis assuming MAR.

6 Discussion

Chained equations multiple imputation is an appealing approach to handling missing data in many data analysis settings. However, the majority of statistical development in this area relies on a key assumption that data are missing at random (MAR). Application of MAR-based imputation and data analysis strategies when data are not missing at random (MNAR) can produce bias in estimating parameters of interest[4].

In this paper, we propose a novel strategy for addressing single variable MNAR missingness *given multiple imputations generated assuming MAR*. MNAR missingness is handled through weighted data analysis applied to the stacked multiple imputations, where the data weights are a function of an assumed model for MNAR missingness. In the special setting where the MNAR missingness mechanism can be reasonably approximated by a standard logistic regression, the weights take a simple form and depend only on a single sensitivity parameter. This parameter has a convenient interpretation as the log-odds ratio association between the MNAR missingness and the true value of the variable with MNAR missingness, adjusting for fully-observed variables. In **Supplementary Section A**, we extend this methodology to handle settings with more complicated MNAR missingness in multiple variables.

The proposed method makes several advances over existing methods in this area. Unlike the related data re-weighting method in Carpenter et al. (2007), the proposed approach defines separate weights for each subject and imputation combination.[7] This prevents estimation from being dominated by a single imputed dataset. As discussed in Rezvan et al. (2015), the method in Carpenter et al. (2007) may also produce inconsistent estimates of common parameters of interest (e.g. means, regression model parameters, etc.) in some cases.[8] This is a result of the reliance on *point estimates* obtained under MAR assumptions, which may be far from the truth. The proposed method uses *imputed data* obtained under MAR assumptions but not the corresponding point estimates, avoiding this challenge and allowing for valid point estimation even under strong MNAR missingness.

Several authors have developed strategies for addressing MNAR missingness *within* the chained equations imputation procedure itself. Tompsett et al. (2018) recommends including missing data indicators as predictors in the imputation model and handles MNAR missingness related to the imputed variable itself through a fixed offset with corresponding sensitivity parameter.[5] This results in a regression model approximation of the "exact" imputation distribution in *Eq. 1*. This approach performed well in simulations when the corresponding offset parameter was well-specified (**Tables C.1 and D.1**). However, imputation *and* data analysis as in Tompsett et al. (2018) must be repeated across multiple values of the sensitivity parameter, which can become computationally challenging for a large grid of plausible values or when the procedure for generating multiple imputations is slow. Our proposed approach also involves repeated analysis across sensitivity parameter values, but it relies on a single set of multiple imputations, avoiding the need to re-impute the data many times. Jolani (2012) avoids use of sensitivity parameters entirely under assumptions that the true model generating missingness follows a logistic regression model with main effects.[6]

However, we found that the implementation of this method in *mice* in R performed poorly in terms of large residual bias in estimating regression model parameters. This may be related to difficulty in identifying parameters in the missingness model and warrants further exploration.

One historical disadvantage of the general strategy of imputation stacking was the limited statistical literature regarding standard error estimation and the lack of corresponding software for easy implementation. However, Beesley and Taylor (2020) recently proposed a simple strategy for estimating standard errors for stacked and weighted multiple imputations (*Eq. 9*) inspired by the observed data information principle in Louis (1982).[16,10] Bernhardt (2019) proposed an alternative strategy involving bootstrapping of multiply imputed data for estimating the between-imputation variation as in *Eq. 10*.[11] Through simulations in **Section 4**, we demonstrate that both general estimation strategies can produce reasonable standard error estimates, with some slight under-coverage (e.g. 90%) seen for the method in *Eq. 9* and some over-coverage seen for the method in Bernhardt (2019) when the MNAR missingness is strong. This under-coverage may be a result of the dependence between the weights (a function of the imputed data) and the target model parameter θ due to the model-based multiple imputation procedure, and future efforts can explore this issue in greater detail. An additional limitation of the proposed approach is that it generally requires more imputed datasets than Rubin's rules-based estimation. The number of required imputations will depend on the amount of missingness, but we generally found good estimation properties for $M = 50$. Given sufficient M and the correct sensitivity parameter, the proposed method resulted in very low bias even for small sample sizes (e.g. $n = 100$).

In the main paper, we focused on the particular setting where we have MNAR missingness in a *single* variable. Missingness in other variables was assumed to be MAR. In **Supplementary Section A**, we extend the proposed method to handle MNAR missingness in *multiple* variables and to allow for more complex MNAR mechanisms. In the special case where (1) missingness in each variable is independent of the true values for other variables with missingness and (2) the MNAR mechanisms are well-approximated with logistic regressions, resulting weights are similar to those in *Eq. 8* but with a separate sensitivity parameter for each variable that is MNAR. In simulations under (1) and (2), this extension performed as expected, with properties similar to those seen in simulations presented here (**Figure E.1**). Future work can explore implementation for more general MNAR missingness.

An overall advantage of the proposed method is that it disentangles the challenges of data imputation (i.e., filling in the missing values) and handling of MNAR (i.e., avoiding or reducing bias due to the MNAR missingness mechanism). This approach can be applied to data previously imputed under MAR assumptions, and point estimation can be very easily implemented using standard software. Standard error estimation presents a greater challenge, and we provide R package *StackImpute* (available at https://github.com/lbeesleyBIOSTAT/StackImpute) to allow users to easily obtain standard errors for many commonly-used regression model settings, including Cox proportional hazards regression and generalized linear models. The primary disadvantage of the proposed methodology is the need to specify values for unidentified sensitivity parameters. This is a common challenge for most MNAR adjustment methods, and existing strategies for eliciting sensitivity parameter values in the pattern mixture modeling literature can be applied to inform reasonable choices for the sensitivity parameters.[18,19] These methods will naturally become more difficult to implement as the dimension of unidentified sensitivity parameters grows, and addressing practical challenges to larger-dimensional sensitivity parameter elicitation is an area for future development.

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Data Availability

Data from illustrative example are not shared due to third-party data sharing restrictions and to protect patient privacy.

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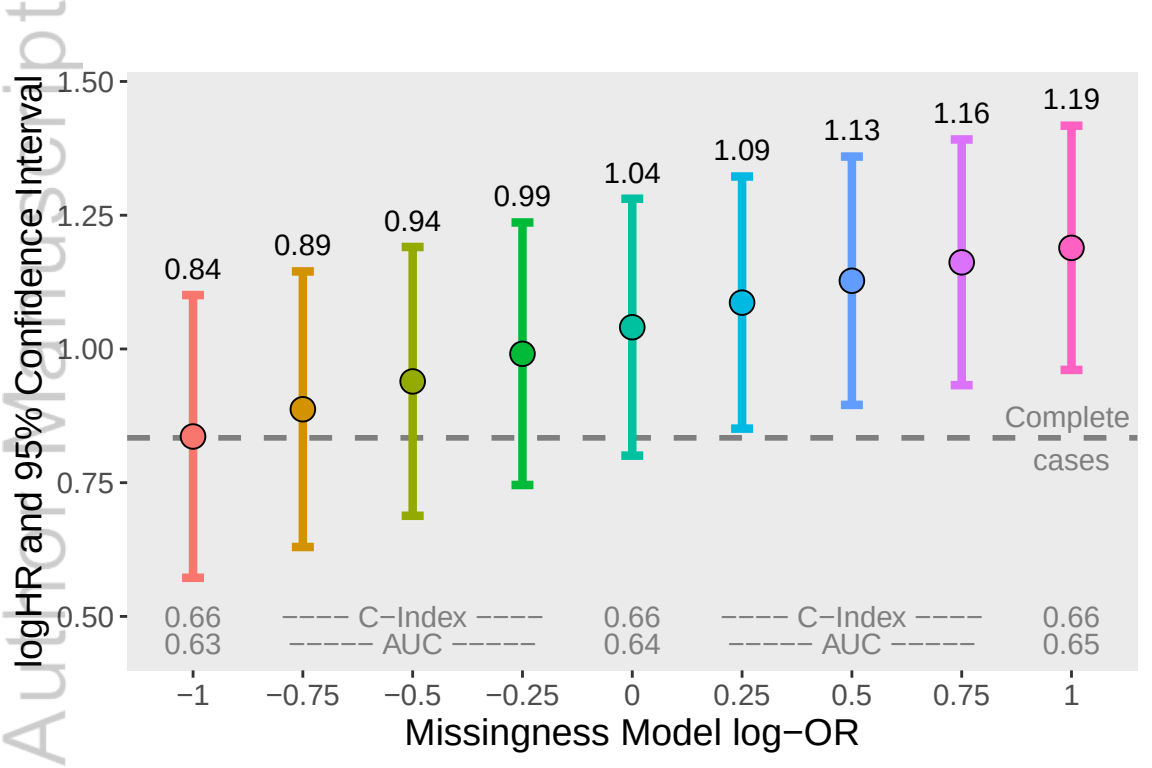

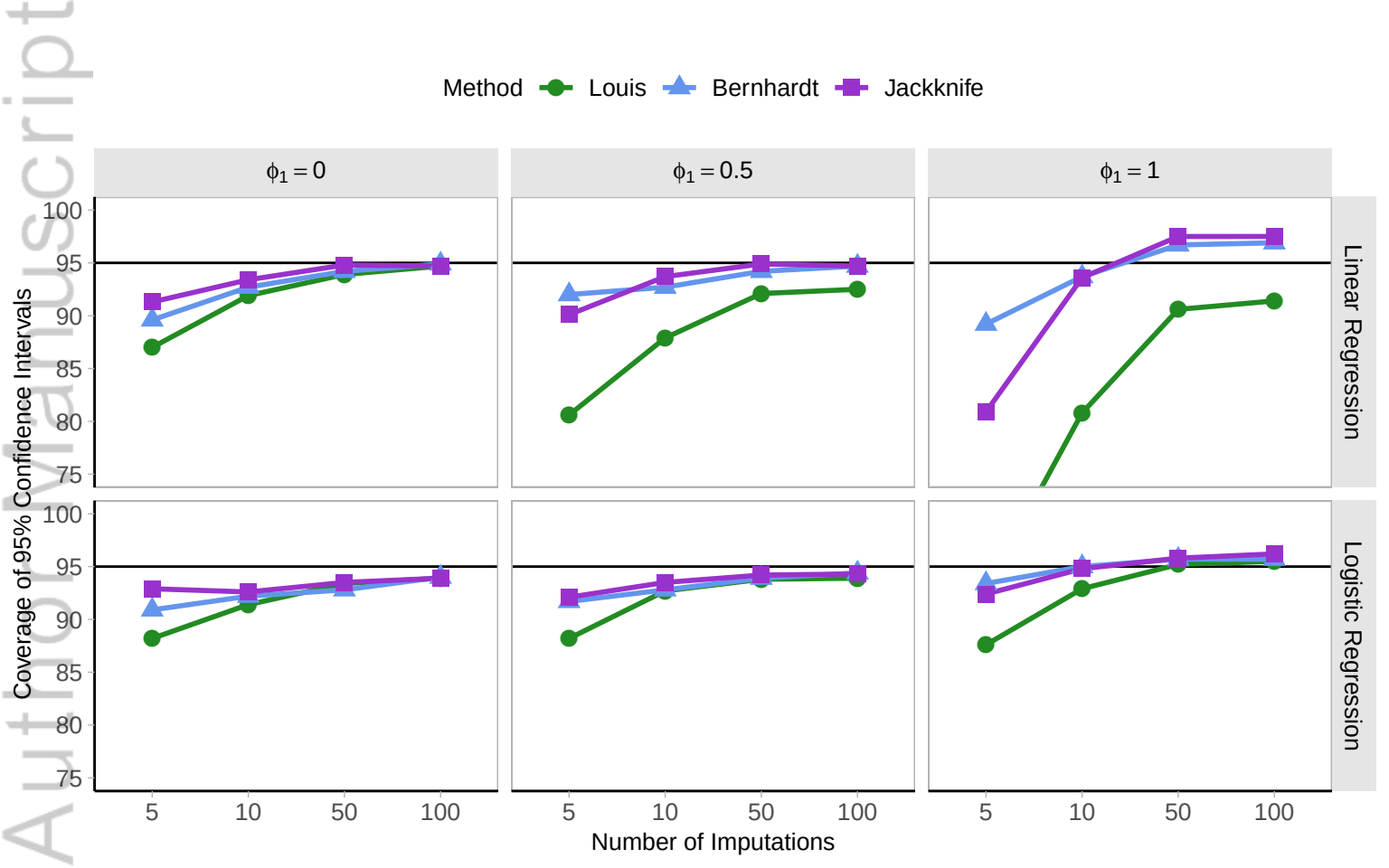

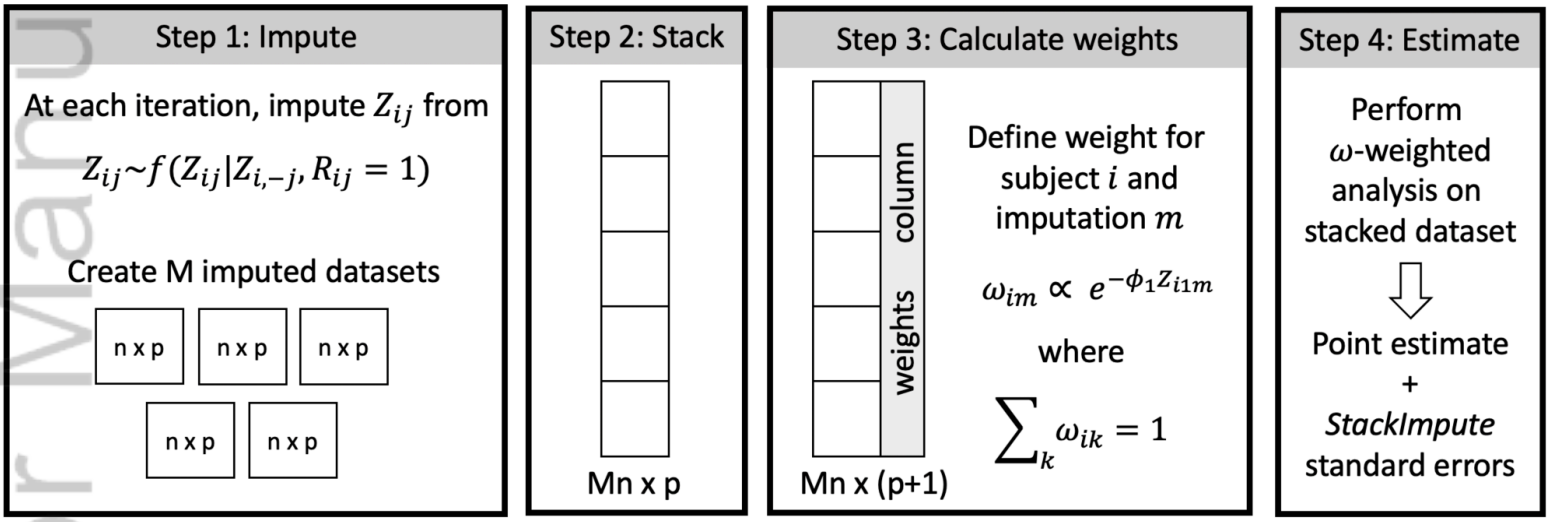

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