# BOOTSTRAP INFERENCE WHEN USING MULTIPLE IMPUTATION

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Many modern estimators require bootstrapping to calculate confidence intervals. It remains however unclear how to obtain valid bootstrap inference when dealing with multiple imputation to address missing data. We present four methods which are intuitively appealing, easy to implement, and combine bootstrap estimation with multiple imputation. We show that only one of the four approaches yield randomization valid confidence intervals. Simulation studies reveal the performance of our approaches in finite samples. A topical analysis from HIV treatment research, which determines the optimal timing of antiretroviral treatment initiation in young children, demonstrates the practical implications of the four methods in a sophisticated and realistic setting.

1. Introduction. Multiple imputation (MI) is currently the most popular method to deal with missing data. Based on assumptions about the data distribution (and the mechanism which gives rise to the missing data) missing values can be imputed by means of draws from the posterior predictive distribution of the unobserved data given the observed data. This procedure is repeated to create M imputed datasets, the analysis is then conducted on each of these datasets and the M results (M point and M variance estimates) are combined by a set of simple rules (Rubin, 1996).

During the last 30 years a lot of progress has been made to make MI available to a variety of settings and areas of research: implementations are available in several software packages (Horton and Kleinman, 2007; Honaker, King and Blackwell, 2011; van Buuren and Groothuis-Oudshoorn, 2011; Royston and White, 2011), review articles provide guidance to deal with practical challenges (White, Royston and Wood, 2011, Sterne et al., 2009, Graham, 2009), non-normal –possibly categorical– variables can often successfully be imputed (Schafer and Graham, 2002, Honaker, King and Blackwell, 2011, White, Royston and Wood, 2011), useful diagnostic tools have been suggested (Honaker, King and Blackwell, 2011, Eddings and Marchenko, 2012), and first attempts to address longitudinal data and other

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complicated data structures have been made (Honaker and King, 2010, van Buuren and Groothuis-Oudshoorn, 2011).

While both opportunities and challenges of multiple imputation are discussed in the literature, we believe an important consideration regarding the inference after imputation has been neglected so far: if there is no analytic or no ideal solution to obtain standard errors for the parameters of the analysis model, and nonparametric bootstrap estimation is used to estimate them, it is unclear how to obtain valid inference – in particular how to obtain appropriate confidence intervals. As we will explain below, many modern statistical concepts, often applied to inform policy guidelines or enhance practical developments, rely on bootstrap estimation. It is therefore inevitable to have guidance for bootstrap estimation for multiply imputed data.

In general, one can distinguish between two approaches for bootstrap inference when using multiple imputation: with the first approach, M imputed datsets are created and bootstrap estimation is applied to each of them; or, alternatively, B bootstrap samples of the original dataset (including missing values) are drawn and in each of these samples the data are multiply imputed. For the former approach one could use bootstrapping to estimate the standard error in each imputed dataset and apply the standard MI combining rules; alternatively, the  $B \times M$  estimates could be pooled and 95% confidence intervals could be calculated based on the  $2.5^{th}$  and  $97.5^{th}$  percentiles of the respective empirical distribution. For the latter approach either multiple imputation combining rules can be applied to the imputed data of each bootstrap sample to obtain B point estimates which in turn may be used to construct confidence intervals; or the  $B \times M$  estimates of the pooled data are used for interval estimation.

To the best of our knowledge, the consequences of using the above approaches have not been studied in the literature before. The use of the bootstrap in the context of missing data has often been viewed as a frequentist alternative to multiple imputation (Efron, 1994), or an option to obtain valid confidence intervals after *single* imputation (Shao and Sitter, 1996). The bootstrap can also be used to create multiple imputations (Little and Rubin, 2002). However, none of these studies have addressed the construction of bootstrap confidence intervals when data needs to be multiply imputed because of missing data. As emphasized above, this is however of particularly great importance when standard errors of the analysis model cannot be calculated easily, for example for causal inference estimators (g-formula), shrinkage and boosting.

It is not surprising that the bootstrap has nevertheless been combined

with multiple imputation for particular analyses. Multiple imputation of bootstrap samples has been implemented in the analyses of Briggs et al. (2006), Schomaker and Heumann (2014); Schomaker et al. (2016), and Worthington, King and Buckland (2014), whereas bootstrapping the imputed datasets was preferred by Wu and Jia (2013), Baneshi and Talei (2012), and Heymans et al. (2007). Other work doesn't offer all details of the implementation (Chaffee, Feldens and Vitolo, 2014). All these analyses give however little justification for the chosen method and for some analyses important details on how the confidence intervals were calculated are missing; it seems that pragmatic reasons as well as computational efficiency typically guide the choice of the approach. None of the studies offer a statistical discussion of the chosen method.

The present article demonstrates the implications of different methods which combine bootstrap inference with multiple imputation. It is novel in that it introduces four different, intuitively appealing, bootstrap confidence intervals for data which require multiple imputation, illustrates their intrinsic features, and argues which of them yield correct conclusions and which not: we show that among the four presented options only one yields valid inference. The other options lead typically to too wide confidence intervals and therefore conservative conclusions.

Section 2 introduces our motivating analysis of causal inference in HIV research. The different methodological approaches are described in detail in Section 3 and are evaluated by means of both numerical investigations (Section 4) and theoretical considerations (Section 5). The implications of the different approaches are further emphasized in the data analysis of Section 6. We conclude in Section 7.

2. Motivation. During the last decade the World Health Organization (WHO) updated their recommendations on the use of antiretroviral drugs for treating and preventing HIV infection several times. In the past, antiretroviral treatment (ART) was only given to a child if his/her measurements of CD4 lymphocytes fell below a critical value or if a clinically severe event (such as tuberculosis or persistent diarrhoea) occurred. Based on both increased knowledge from trials and causal modeling studies, as well as pragmatic and programmatic considerations, these criteria have been gradually expanded to allow earlier treatment initiation in children: since 2013 all children who present under the age of 5 are treated immediately, while for older children CD4-based criteria still exist. ART has shown to be effective and to reduce mortality in infants and adults (Westreich et al., 2012, Edmonds et al., 2011, Violari et al., 2008), but concerns remain due to a potentially

increased risk of toxicities, early development of drug resistance, and limited future options for people who fail treatment. By the end of 2015 WHO decided to recommend immediate treatment initiation in all children and adults.

It remains therefore important to investigate the effect of different treatment initiation rules on mortality, morbidity and child development outcomes; however given the shift in ART guidelines towards earlier treatment initiation it is not ethically possible anymore to conduct a trial which answers this question in detail. Thus, observational data can be used to obtain the relevant estimates. Methods such as inverse probability weighting of marginal structural models, the g-computation formula, and targeted maximum likelihood estimation can be used to obtain estimates in complicated longitudinal settings where time-varying confounders affected by prior treatment are present — such as, for example, CD4 count which influences both the probability of ART initiation and outcome measures (Daniel et al., 2013, Petersen et al., 2014).

In situations where treatment rules are dynamic, i.e. where they are based on a time-varying variable such as CD4 lymphocyte count, the g-computation formula (Robins, 1986) is the intuitive method to use. It is computationally intensive and allows the comparison of outcomes for different treatment options; confidence intervals are typically based on non-parametric bootstrap estimation. However, in resource limited settings data may be missing for administrative, logistic, and clerical reasons, as well as due to loss to follow-up and missed clinic visits. Depending on the underlying assumptions about the reasons for missing data this problem can either be addressed by the g-formula directly or by using multiple imputation. However, it is not immediately clear how to combine multiple imputation with bootstrap estimation too obtain valid confidence intervals.

3. Methodological Framework. Let  $\mathcal{D}$  be a  $n \times (p+1)$  data matrix consisting of an outcome variable  $\mathbf{y} = (y_1, \ldots, y_n)'$  and covariates  $\mathbf{X}_{\mathbf{j}} = (X_{1j}, \ldots, X_{nj})'$ ,  $j = 1, \ldots, p$ . The  $1 \times p$  vector  $\mathbf{x}_i = (x_{i1}, \ldots, x_{ip})$  contains the  $i^{th}$  observation of each of the p covariates and  $\mathbf{X} = (\mathbf{x}_1', \ldots, \mathbf{x}_n')'$  is the matrix of all covariates. Suppose we are interested in estimating  $\theta = (\theta_1, \ldots, \theta_k)'$ ,  $k \geq 1$ , which may be any function of  $\mathbf{X}$  and  $\mathbf{y}$ ,  $\theta = \theta(\mathbf{X}, \mathbf{y})$ , such as a regression coefficient, an odds ratio, a factor loading, or a counterfactual outcome. If some data are missing, making the data matrix to consist of both observed and missing values,  $\mathcal{D} = \{\mathcal{D}^{\text{obs}}, \mathcal{D}^{\text{mis}}\}$ , and the missingness mechanism is ignorable, valid inference for  $\theta$  can be obtained using multiple imputation. Following Rubin (1996) we regard valid inference to mean

that the point estimate  $\hat{\theta}$  for  $\theta$  is approximately unbiased and that interval estimates are randomization valid in the sense that actual interval coverage equals the nominal interval coverage.

Under multiple imputation M augmented sets of data are generated, and the imputations (which replace the missing values) are based on draws from the predictive posterior distribution of the missing data given the observed data  $p(\mathcal{D}^{\text{mis}}|\mathcal{D}^{\text{obs}}) = \int p(\mathcal{D}^{\text{mis}}|\mathcal{D}^{\text{obs}};\vartheta) \ p(\vartheta|\mathcal{D}^{\text{obs}}) \ d\vartheta$ , or an approximation thereof. The point estimate for  $\theta$  is

$$\hat{\bar{\theta}}_{\text{MI}} = \frac{1}{M} \sum_{m=1}^{M} \hat{\theta}_m$$

where  $\hat{\theta}_m$  refers to the estimate of  $\theta$  in the m<sup>th</sup> imputed set of data  $\mathcal{D}^{(m)}$ ,  $m=1,\ldots,M$ . Variance estimates can be obtained using the between imputation covariance  $\hat{B}=(M-1)^{-1}\sum_{m}(\hat{\theta}_m-\hat{\theta}_{\mathrm{MI}})(\hat{\theta}_m-\hat{\theta}_{\mathrm{MI}})'$  and the average within imputation covariance  $\widehat{W}=M^{-1}\sum_{m}\widehat{\mathrm{Cov}}(\hat{\theta}_m)$ :

$$(3.2) \qquad \widehat{\operatorname{Cov}}(\widehat{\theta}_{\mathrm{MI}}) = \widehat{W} + \frac{M+1}{M}\widehat{B} = \frac{1}{M} \sum_{m=1}^{M} \widehat{\operatorname{Cov}}(\widehat{\theta}_{m}) + \frac{M+1}{M(M-1)} \sum_{m=1}^{M} (\widehat{\theta}_{m} - \widehat{\theta}_{\mathrm{MI}})(\widehat{\theta}_{m} - \widehat{\theta}_{\mathrm{MI}})'.$$

For the scalar case this equates to

$$\widehat{\operatorname{Var}}(\widehat{\hat{\theta}}_{\mathrm{MI}}) = \frac{1}{M} \sum_{m=1}^{M} \widehat{\operatorname{Var}}(\widehat{\theta}_{m}) + \frac{M+1}{M(M-1)} \sum_{m=1}^{M} (\widehat{\theta}_{m} - \widehat{\bar{\theta}}_{\mathrm{MI}})^{2}.$$

To construct confidence intervals for  $\hat{\theta}_{\rm MI}$  in the scalar case, it may be assumed that  $\widehat{\rm Var}(\hat{\theta}_{\rm MI})^{-\frac{1}{2}}(\hat{\theta}_{\rm MI}-\theta)$  follows a  $t_R$ -distribution with approximately  $R=(M-1)[1+\{M\hat{W}/(M+1)\hat{B}\}]^2$  degrees of freedom (Rubin and Schenker, 1986), though there are alternative approximations, especially for small samples.

Consider the situation where there is no analytic or no ideal solution to estimate  $Cov(\hat{\theta}_m)$ , for example when using particular shrinkage estimators (Tibsharani, 1996, Wang et al., 2011, Schomaker, 2012), implementing boosting (Bühlmann, 2006), or estimating the treatment effect in the presence of time-varying confounders affected by prior treatment using gmethods (Robins and Hernan, 2009, Daniel et al., 2013). If there are no missing data, bootstrap percentile confidence intervals may offer a solution:

based on B bootstrap samples  $\mathcal{D}_b^*$ ,  $b=1,\ldots,B$ , we obtain B point estimates  $\hat{\theta}_b^*$ . Consider the ordered set of estimates  $\Theta_B^* = \{\hat{\theta}_{(b)}^*; b=1,\ldots,B\}$ , where  $\hat{\theta}_{(1)}^* < \hat{\theta}_{(2)}^* < \ldots < \hat{\theta}_{(B)}^*$ ; the bootstrap  $1-2\alpha\%$  confidence interval for  $\theta$  is then defined as

$$[\hat{\theta}_{lower}; \hat{\theta}_{upper}] = [\hat{\theta}^{*,\alpha}; \hat{\theta}^{*,1-\alpha}]$$

where  $\hat{\theta}^{*,\alpha}$  denotes the  $\alpha$ -percentile of the ordered bootstrap estimates  $\Theta_B^*$ . However, in the presence of missing data the construction of confidence intervals is not immediately clear as  $\hat{\theta}$  corresponds to M estimates  $\hat{\theta}_1, \dots, \hat{\theta}_M$ . It seems intuitive to consider the following four approaches:

• Method 1, MI Boot pooled: Multiple imputation is utilized for the dataset  $\mathcal{D} = \{\mathcal{D}^{\text{obs}}, \mathcal{D}^{\text{mis}}\}$ . For each of the M imputed datasets  $\mathcal{D}_m$ , B bootstrap samples are drawn which yields  $M \times B$  datasets  $\mathcal{D}_{m,b}^*; b = 1, \ldots, B; m = 1, \ldots, M$ . In each of these datasets the quantity of interest is estimated, that is  $\hat{\theta}_{m,b}^*$ . The pooled set of ordered estimates  $\Theta_{\text{MIBP}}^* = \{\hat{\theta}_{(m,b)}^*; b = 1, \ldots, B; m = 1, \ldots, M\}$  is used to construct the  $1 - 2\alpha\%$  confidence interval for  $\theta$ :

$$[\hat{\theta}_{lower}; \hat{\theta}_{upper}]_{MIBP} = [\hat{\theta}_{MIBP}^{*,\alpha} \hat{\theta}_{MIBP}^{*,1-\alpha}]$$

where  $\hat{\theta}_{\text{MIBP}}^{*,\alpha}$  is the  $\alpha$ -percentile of the ordered bootstrap estimates  $\Theta_{\text{MIBP}}^*$ .

- Method 2, MI Boot: Multiple imputation is utilized for the dataset  $\mathcal{D} = \{\mathcal{D}^{\text{obs}}, \mathcal{D}^{\text{mis}}\}$ . For each of the M imputed datasets  $\mathcal{D}_m$ , B bootstrap samples are drawn which yields  $M \times B$  datasets  $\mathcal{D}_{m,b}^*$ ;  $b = 1, \ldots, B$ ;  $m = 1, \ldots, M$ . The bootstrap samples are used to estimate the standard error of (each scalar component of)  $\hat{\theta}_m$  in each imputed dataset respectively, i.e.  $\widehat{\text{Var}}(\hat{\theta}_m) = (B-1)^{-1} \sum_b (\hat{\theta}_{m,b} \hat{\bar{\theta}}_{m,b})^2$  with  $\hat{\bar{\theta}}_{m,b} = B^{-1} \sum_b \hat{\theta}_{m,b}$ . This results in M point estimates and M standard errors related to the M imputed datasets. More generally,  $\text{Cov}(\hat{\theta}_m)$  can be estimated in each imputed dataset using bootstrapping, thus allowing the use of (3.2) and standard multiple imputation confidence interval construction, possibly based on a  $t_R$ -distribution.
- Method 3, Boot MI pooled: B bootstrap samples  $\mathcal{D}_b^*$  (including missing data) are drawn and multiple imputation is utilized in each bootstrap sample. Therefore, there are  $B \times M$  imputed datasets  $\mathcal{D}_{b,1}^*, \ldots, \mathcal{D}_{b,M}^*$  which can be used to obtain the corresponding point

estimates  $\hat{\theta}_{b,m}^*$ . The set of the pooled ordered estimates  $\Theta_{\text{BMIP}}^* = \{\hat{\theta}_{(b,m)}^*; b = 1, \dots, B; m = 1, \dots, M\}$  can then be used to construct the  $1 - 2\alpha\%$  confidence interval for  $\theta$ :

$$[\hat{\theta}_{lower}; \hat{\theta}_{upper}]_{BMIP} = [\hat{\theta}_{BMIP}^{*,\alpha}; \hat{\theta}_{BMIP}^{*,1-\alpha}]$$

where  $\hat{\theta}_{\text{BMIP}}^{*,\alpha}$  is the  $\alpha$ -percentile of the ordered bootstrap estimates  $\Theta_{\text{BMIP}}^*$ .

• Method 4, Boot MI: B bootstrap samples  $\mathcal{D}_b^*$  (including missing data) are drawn, and each of them is imputed M times. Therefore, there are M imputed datasets,  $\mathcal{D}_{b,1}^*, \ldots, \mathcal{D}_{b,M}^*$ , which are associated with each bootstrap sample  $\mathcal{D}_b^*$ . They can be used to obtain the corresponding point estimates  $\hat{\theta}_{b,m}^*$ . Thus, applying (3.1) to the estimates of each bootstrap sample yields B point estimates  $\hat{\theta}_b^* = M^{-1} \sum_m \hat{\theta}_{b,m}^*$  for  $\theta$ . The set of ordered estimates  $\Theta_{\text{BMI}}^* = \{\hat{\theta}_{(b)}^*; b = 1, \ldots, B\}$  can then be used to construct the  $1 - 2\alpha\%$  confidence interval for  $\theta$ :

$$[\hat{\theta}_{lower}; \hat{\theta}_{upper}]_{BMI} = [\hat{\theta}_{BMI}^{*,\alpha}; \hat{\theta}_{BMI}^{*,1-\alpha}]$$

where  $\hat{\theta}_{\text{BMI}}^{*,\alpha}$  is the  $\alpha$ -percentile of the ordered bootstrap estimates  $\Theta_{\text{BMI}}^*$ .

While all of the methods described above are straightforward to implement it is unclear if they yield valid inference, i.e. if the actual interval coverage level equals the nominal coverage level. Before we delve into some theoretical considerations we expose some of the intrinsic features of the different interval estimates using Monte Carlo simulations.

4. Simulation Studies. To study the finite sample performance of the methods introduced above we consider two simulation settings: a simple one, to ensure that these comparisons are not complicated by the simulation setup; and a more complicated one, to study the four methods under a more sophisticated variable dependence structure.

Setting 1: We simulate a normally distributed variable  $X_1$  with mean 0 and variance 1. We then define  $\mu_y = 0 + 0.4X_1$  and  $\theta = \beta_{\text{true}} = (0, 0.4)'$ . The outcome is generated from  $N(\mu_y, 2)$  and the analysis model of interest is the linear model. Values of  $X_1$  are defined to be missing with probability

$$\pi_{X_1}(y) = 1 - \frac{1}{(0.25y)^2 + 1}.$$

With this, about 16% of values of  $X_1$  were missing (at random). Since the probability of a value to be missing depends on the outcome, one would expect parameter estimates in a regression model of a complete case analysis to be biased, but estimates following multiple imputation to be approximately unbiased (Little, 1992).

Setting 2: The observations for 6 variables are generated using the following normal and binomial distributions:  $\mathbf{X}_1 \sim \mathrm{N}(0,1), \ \mathbf{X}_2 \sim \mathrm{N}(0,1), \ \mathbf{X}_3 \sim \mathrm{N}(0,1), \ \mathbf{X}_4 \sim \mathrm{B}(0.5), \ \mathbf{X}_5 \sim \mathrm{B}(0.7), \ \mathrm{and} \ \mathbf{X}_6 \sim \mathrm{B}(0.3).$  To model the dependency between the covariates we use a Clayton Copula (Yan, 2007) with a copula parameter of 1 which indicates moderate correlation among the covariates. We then define  $\mu_y = 3 - 2X_1 + 3X_3 - 4X_5$  and  $\theta = \beta_{\mathrm{true}} = (3, -2, 0, 3, 0, -4, 0)'$ . The outcome is generated from  $N(\mu_y, 2)$  and the analysis model of interest is the linear model. Values of  $X_1$  and  $X_3$  are defined to be missing (at random) with probability

$$\pi_{X_1}(y) = 1 - \frac{1}{(0.25y)^2 + 1}, \qquad \pi_{X_3}(X_4) = 1 - \frac{1}{0.25X_4 + 1.05}.$$

This yields about 6% and 14% of missing values for  $X_1$  and  $X_3$  respectively. In both settings multiple imputation is utilized with Amelia II under a joint modeling approach, see Honaker, King and Blackwell (2011) for details.<sup>1</sup>

We estimate the confidence intervals for  $\beta$  using the aforementioned four approaches, as well as using the analytic standard errors obtained from the linear model (method "no bootstrap"). We generate n=1000 observations, B=200 bootstrap samples, and M=10 imputations. Based on  $\mathcal{R}=1000$  simulation runs we evaluate the bias and distribution of  $\beta$  for the different methods, as well as the coverage probability and median width of the respective confidence intervals.

Results: In both settings point estimates for  $\beta$  were approximately unbiased. Table 1 summarizes the main results of the simulations. Using no bootstrapping to estimate the standard errors in the linear model, and applying

<sup>&</sup>lt;sup>1</sup>Briefly, one assumes a multivariate normal distribution for the data,  $\mathcal{D} \sim N(\mu, \Sigma)$  (possibly after suitable transformations beforehand). Then, B bootstrap samples of the data (including missing values) are drawn and in each bootstrap sample the EM algorithm (Dempster, Laird and Rubin, 1977) is applied to obtain estimates of  $\mu$  and  $\Sigma$  which can then be used to generate proper multiple imputations by means of the sweep-operator (Goodnight, 1979, Honaker and King, 2010). Of note, the algorithm can handle highly skewed variables by imposing transformations on variables (log, square root) and recodes categorical variables into dummies based on the knowledge that for binary variables the multivariate normal assumption can yield good results (Schafer and Graham, 2002).

Table 1
Results of the simulation studies: estimated coverage probability (top), median confidence intervals width (middle), and standard errors for different methods

		Method	Setting 1	Setting 2					
			$\beta_1$	$\beta_1$	$\beta_2$	$\beta_3$	$\beta_4$	$\beta_5$	$\beta_6$
Coverage	Probability	MI Boot (pooled)	100%	100%	100%	100%	100%	100%	100%
		MI Boot	100%	100%	100%	100%	100%	100%	100%
		Boot MI	95%	94%	94%	94%	94%	94%	95%
		Boot MI (pooled)	97%	95%	96%	96%	96%	96%	96%
		no bootstrap	95%	95%	95%	95%	95%	95%	95%
Median	CI Width	MI Boot (pooled)	2.48	4.53	4.60	4.45	7.51	8.50	7.42
		MI Boot	1.46	3.04	3.05	3.03	5.00	5.59	4.75
		Boot MI	0.31	0.33	0.33	0.33	0.60	0.67	0.62
		Boot MI (pooled)	0.35	0.36	0.35	0.35	0.64	0.72	0.66
		no bootstrap	0.31	0.34	0.34	0.34	0.61	0.69	0.63
Std.	Error	simulated	0.08	0.09	0.09	0.09	0.15	0.17	0.15
		no bootstrap	0.08	0.09	0.09	0.09	0.16	0.18	0.16
		MI Boot	0.39	1.56	1.29	1.15	2.12	2.00	1.47

the standard multiple imputation rules (3.1) and (3.2), yields estimated coverage probabilities of 95%, for all parameters and settings.

Bootstrapping the imputed data (MI Boot, MI Boot pooled) yields estimated coverage probabilities of 100% and confidence interval widths which are often 10 times higher than the widthes under no bootstrap estimation. This is also highlighted in the evaluation of the simulated and estimated standard errors: The standard errors of  $\beta$  as simulated in the 1000 simulation runs were almost identical to the mean estimated standard errors under no bootstrap estimation; however bootstrapping of the imputed data led to unacceptably high estimated standard errors. We explain in Section 5 why this is the case.

Imputing the bootstrapped data (Boot MI, Boot MI pooled) led to overall better results with coverage probabilities close to the nominal level; however, using the pooled approach led to somewhat higher coverage probabilities and the interval widths were clearly different from the estimates obtained under no bootstrapping.

Figure 1 highlights that imputing the bootstrapped data yields a distribution of  $\beta$  which is similar to the simulated one. It is also evident that bootstraping the imputed data (MI Boot) yields a much wider distribution, even within each imputed dataset (Figure 2).

The results were not affected by changing the sample size, the missingness probability, the effect size, or dependency structure. However, if the imputation model was not able to capture the complexity of non-linear relationships

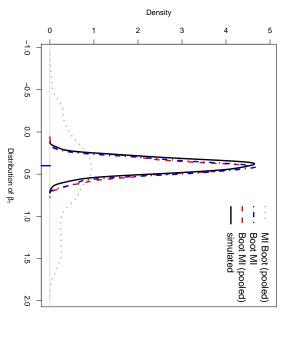


Fig 1: Distribution of  $\beta_1$  in the first simulation setting: the simulated distribution ( $\mathcal{R}=1000$  simulation runs) is contrasted with the estimated distribution of (i) MI Boot (pooled), (ii) Boot MI, and (iii) Boot MI (pooled) in a random simulation run

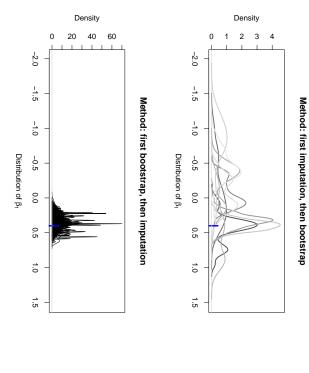


Fig 2: Distribution of  $\beta_1$  in the first simulation setting: for MI Boot the estimated distribution in each imputed dataset is shown (top), and for Boot MI the distributions across multiple imputations is shown for the different bootstrap samples (bottom)

among the variables, parameter estimates were biased, and consequently nominal coverage was not achieved with the Boot MI method.

5. Theoretical Considerations. For the purpose of inference we are interested in the observed data posterior distribution of  $\theta | \mathcal{D}_{obs}$  which is

$$P(\theta|\mathcal{D}_{obs}) = \int P(\theta|\mathcal{D}_{obs}, \mathcal{D}_{mis}) P(\mathcal{D}_{mis}|\mathcal{D}_{obs}) d\mathcal{D}_{mis}$$

$$(5.1) = \int P(\theta|\mathcal{D}_{obs}, \mathcal{D}_{mis}) \left\{ \int P(\mathcal{D}_{mis}|\mathcal{D}_{obs}, \vartheta) P(\vartheta|\mathcal{D}_{obs}) d\vartheta \right\} d\mathcal{D}_{mis}.$$

Please note that  $\vartheta$  refers to the parameters of the imputation model whereas  $\theta$  is the quantity of interest from the analysis model. With multiple imputation we effectively approximate the integral (5.1) by using the average

(5.2) 
$$P(\theta|\mathcal{D}_{obs}) \approx \frac{1}{M} \sum_{m=1}^{M} P(\theta|\mathcal{D}_{mis}^{(m)}, \mathcal{D}_{obs})$$

where  $\mathcal{D}_{mis}^{(m)}$  refers to draws (imputations) from the posterior predictive distribution  $P(\mathcal{D}_{mis}|\mathcal{D}_{obs})$ .

Bootstrapping the Imputed Data. Now suppose we are bootstrapping multiply imputed data to obtain the estimates MI Boot as explained in Section 3. In this case, we draw the bootstrap samples from  $\{\mathcal{D}_{mis}^{(m)}, \mathcal{D}_{obs}\}$ , and not  $\mathcal{D} = \{\mathcal{D}_{mis}, \mathcal{D}_{obs}\}$ , which follows its own multivariate distribution  $\mathcal{P}_m^*$ . The variance estimates obtained from the imputed datasets using bootstrapping are  $\widehat{Var}(\hat{\theta}^{(m)}|\mathcal{D}_{mis}^{(m)},\mathcal{D}_{obs})$ ,  $m=1,\ldots,M$  and are therefore conditional on the m<sup>th</sup> imputation draw. These estimates are not identical to  $\widehat{Var}(\hat{\theta}|\mathcal{D}_{obs})$  which we need to apply (3.2). Combining the M estimates is not meaningful because the quantity we use in our calculation is not  $\theta$  but rather M different quantities  $\theta_m$  which are all not unconditional on the missing and imputed data.

More general, the bootstrap sample is conditional on the imputed data which is generated by *one* draw of  $\vartheta^{(m)}$  from its posterior distribution  $P(\vartheta|\mathcal{D}_{obs})$  and *one* draw from  $P(\mathcal{D}_{mis}|\mathcal{D}_{obs},\vartheta^{(m)})$  given  $\vartheta^{(m)}$ . We therefore do not integrate  $\vartheta$  out, but rather estimate

$$P(\theta|\mathcal{D}_{obs}, \mathcal{D}_{mis}^{(m)})|\{\mathcal{D}_{mis}^{(m)}|\mathcal{D}_{obs}, \vartheta^{(m)}\}$$

which is in general not identical to (5.1) and therefore does not estimate  $P(\theta|\mathcal{D}_{obs})$ . Combining M of the above estimates means dealing with the

uncertainty of M different estimates  $\hat{\theta}^{(m)}$  rather than only one estimate  $\theta$  which explains why the variance of the MI Boot methods is typically too large: each  $\theta_m$  refers to its own imputed dataset  $\{\mathcal{D}_{mis}^{(m)}, \mathcal{D}_{obs}\}$  with its own estimated variability conditional on the imputed values.

Imputing the Bootstrapped Data. As opposed to the above methods, Boot MI uses  $\mathcal{D} = \{\mathcal{D}_{mis}, \mathcal{D}_{obs}\}$  for bootstrapping. Most importantly, we estimate  $\theta$ , the quantity of interest, in each bootstrap sample using multiple imputation. We therefore approximate  $P(\theta|D_{obs})$  through (5.1) by using multiple imputation to obtain  $\theta$  and bootstrapping to estimate its distribution. However, if we pool the data, our focus shifts from  $\theta$  to  $\theta_m$ : effectively each of the  $B \times M$  estimates  $\theta_m$  serves as an estimator of  $\theta$ . Since we do not average the M estimates in each of the B bootstrap samples we have  $B \times M$ estimators  $\hat{\theta}_{\text{MI}} = \frac{1}{M} \sum_{m=1}^{M} \hat{\theta}_{m}$  with M = 1, i.e.  $\hat{\theta}_{\text{MI}} = \frac{1}{1} \sum_{m=1}^{1} \hat{\theta}_{m}$ . These estimators are inefficient as we know from MI theory: the efficiency of an MI based estimator is  $(1 + \frac{\gamma}{M})^{-1}$  where  $\gamma$  describes the fraction of missingness in the data. The lower M, the lower the efficiency, and thus the higher the variance. This explains the results of the simulation studies: pooling the estimates is not wrong in itself, but inefficient. We thus typically get larger interval estimates when pooling instead of using the Boot MI method. Note that comparisons between MI Boot pooled and Boot MI pooled are difficult because the within and between imputation uncertainty, as well as the within and between bootstrap sampling uncertainty, will determine the actual width of an confidence interval. The below data example is going to illustrate this point.

6. Data Analysis. Consider the motivating question introduced in Section 2. We are interested in comparing mortality with respect to different antiretroviral treatment strategies in children between 1 and 5 years of age living with HIV. We use data from two big HIV treatment cohort collaborations (IeDEA-SA, Egger et al. (2012); IeDEA-WA, Ekouevi et al. (2011)) and evaluate mortality for 3 years of follow-up. Our analysis builds on a recently published analysis by Schomaker et al. (2016).

For this analysis, we are particularly interested in the cumulative mortality at 36 months of follow-up for the strategy 'immediate ART initiation' and the cumulative mortality difference between strategies (i) 'immediate ART initiation' and (ii) 'assign ART if CD4 count  $< 350 \text{ cells/mm}^3$  or CD4% < 15%', i.e. we are comparing current practices with those in place in 2006. We can estimate these quantities using the g-formula, see Appendix A for a comprehensive summary of our implementation details. The standard way to obtain 95% confidence intervals for this method is using bootstrapping.

However, baseline data of CD4 count, CD4%, HAZ, and WAZ are missing: 18%, 28%, 40%, and 25% respectively. We use multiple imputation (Amelia II, Honaker, King and Blackwell, 2011, described in the simulation section) to impute this data. We also impute follow-up data after nine months without any visit data, as from there on it is plausible that follow-up measurements that determine ART assignment (e.g. CD4 count) were taken (and are thus needed to adjust for time-dependent confounding) but were not electronically recorded, probably because of clerical and administrative errors. Under different assumptions imputation may not be needed. To combine the M=10 imputed datasets with bootstrap estimation (B=200) we use the four approaches introduced in Section 3: MI Boot, MI Boot pooled, Boot MI, and Boot MI pooled.

Three year mortality for immediate ART initiation was estimated as 6.08%, whereas mortality for strategy (ii) was estimated as 6.87%. This implies a mortality difference of 0.79%. The results of the respective confidence intervals are summarized in Figures 3-6: for absolute mortality the intervals are [5.08%; 7.31%] for Boot MI pooled, [5.37%; 7.01%] for Boot MI, [5.22%; 7.90%] for MI Boot pooled, and [4.46%; 7.69%] for MI Boot. For the mortality difference the estimates are are [-0.34%; 1.61%] for Boot MI pooled, [0.12%; 1.07%] for Boot MI, [-0.31%; 1.63%] for MI Boot pooled, and [-0.81%; 2.40%] for MI Boot

Figures 3 and 4 show that, as in the simulations, the confidence intervals are the widest for the approaches which impute first and then bootstrap the imputed data (MI Boot, MI Boot pooled). The shortest interval is produced by the method Boot MI. Note that only for this method the 95% confidence interval does not contain the 0% when estimating the mortality difference, and therefore suggests a beneficial effect of immediate treatment intiation. The bootstrap distribution of all estimators is reasonably symmetric.

Figure 5 visualizes both the bootstrap distributions in each imputed dataset (method MI Boot pooled) as well as the distribution of the estimators in each bootstrap sample (method Boot MI pooled). It is evident that the variation of the estimates is overall higher for the former approach. Interestingly, when focusing on the the cumulative mortality difference rather than the cumulative mortality (Figure 6), this is not the case: the variation of the estimates is similar for the two approaches considered. As discussed earlier, depending on both within and between imputation and bootstrap sampling uncertainty the width of the confidence intervals is determined.

In summary, the above analyses suggest a beneficial effect of immediate ART initiation compared to delaying ART until CD4 count  $< 350 \text{ cells/mm}^3$  or CD4% < 15% when using method 3, Boot MI.

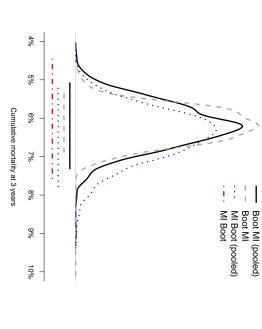


Fig 3: Estimated cumulative mortality at 3 years for the intervention 'immediate ART': distributions and confidence intervals of different estimators

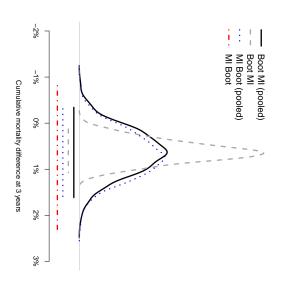


Fig 4: Estimated cumulative mortality difference between the interventions 'immediate ART' and '350/15' at 3 years: distributions and confidence intervals of different estimators

0.03

0.02

0.01

0.03

0.02

0.01

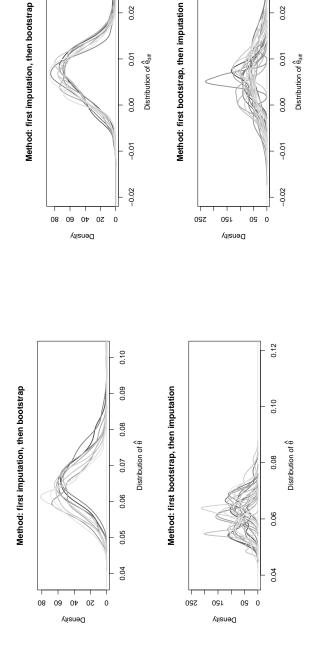


Fig 5: Estimated cumulative mortality at 3 years for the intervention 'immediate ART': distribution of 'MI Boot (pooled)' for each imputed dataset (top) and distribution of 'Boot MI (pooled)' for 25 random bootstrap samples.

Fig 6: Estimated cumulative mortality difference: distribution of 'MI Boot (pooled)' for each imputed dataset (top) and distribution of 'Boot MI (pooled)' for 25 random bootstrap samples (bottom).

The other methods produce larger confidence intervals and do not necessarily suggest a mortality difference which highlights the importance of choosing the right method to construct the interval.

7. Conclusion. The current statistical literature is not clear on how to combine bootstrap with multiple imputation inference. We have proposed that a number of approaches are intuitively appealing, but only one provides efficient and randomization valid confidence intervals; that is to bootstrap the data including missing values, to multiply impute each bootstrap sample, and to use the MI estimates in each bootstrap sample (i.e. the average of the M estimates) as a basis to construct nonparametric bootstrap percentile confidence intervals. These findings are of particular interest when implementing the g-computation formula because bootstrapping is required to calculate confidence intervals. Our analysis demonstrates that the effects of policy interventions may remain hidden if confidence intervals are not constructed in the right way.

#### APPENDIX A: DETAILS OF THE G-FORMULA IMPLEMENTATION

We consider n children studied at baseline (t = 0) and during discrete follow-up times (t = 1, ..., T). The data  $\mathcal{D} = \{\mathbf{y}, \mathbf{X}\}$  consists of the outcome  $\mathbf{y}_t$ , and covariate data  $\mathbf{X}_t = \{\mathbf{A}_t, \mathbf{L}_t, \mathbf{V}_t, \mathbf{C}_t, \mathbf{M}_t\}$  comprising an intervention variable  $\mathbf{A}_t$ , q time-dependent covariates  $\mathbf{L}_t = \{\mathbf{L}_t^1, ..., \mathbf{L}_t^q\}$ , an administrative censoring indicator  $\mathbf{C}_t$ , a censoring due to loss to follow-up (drop-out) indicator  $\mathbf{M}_t$ , and baseline variables  $\mathbf{V} = \{\mathbf{L}_0^1, ..., \mathbf{L}_0^{q_V}\}$ . The treatment and covariate history of an individual i up to and including time t is represented as  $\bar{\mathbf{A}}_{t,i} = (A_{0,i}, ..., A_{t,i})$  and  $\bar{\mathbf{L}}_{t,i}^s = (L_{0,i}^s, ..., L_{t,i}^s)$ ,  $s \in \{1, ..., q\}$ , respectively.  $C_t$  equals 1 if a subject gets censored in the interval (t-1,t], and 0 otherwise. Therefore,  $\bar{C}_t = 0$  is the event that an individual remains uncensored until time t. The same notation is used for  $M_t$  and  $\bar{M}_t$ .

Let  $\mathbf{L}_{t+1}^*$  be the covariates which had been observed under a dynamic intervention rule  $d_t^* = d_t^*(\bar{\mathbf{L}}_t)$  which assigns treatment  $A_{t,i} \in \{0,1\}$  as a function of the covariates  $\bar{\mathbf{L}}_{t,i}^s$ . The counterfactual outcome  $\mathbf{Y}_{(\bar{a}^*,t,i)}$  refers to the hypothetical outcome that would have been observed at time t if a subject i had received, likely contrary to the fact, the treatment history  $\bar{\mathbf{A}}_t = \bar{\mathbf{a}}_t^*$  related to rule  $d_t^*$ .

In our setting we study n = 5826 children for  $t = 0, 1, 3, 6, 9, \ldots$  where the follow-up time points refer to the intervals (0, 1.5), [1.5, 4.5), [4.5, 7.5), ..., [28.5, 31.5), [31.5, 36) months respectively. Follow-up measurements, if available, refer to measurements closest to the middle of the interval. In our data  $\mathbf{y}_t$  refers to death at time t (i.e. occurring during the interval (t - 1, t]),  $\mathbf{A}_t$ 

refers to antiretroviral treatment (ART) taken at time t,  $\mathbf{L}_t = (\mathbf{L}_t^1, \mathbf{L}_t^2, \mathbf{L}_t^3)$  refer to CD4 count, CD4%, and weight for age z-score (WAZ)(which serves as a proxy for WHO stage, see Schomaker et al. (2013) for more details),  $\mathbf{V} = \mathbf{L}_0^V$  refer to baseline values of CD4 count, CD4%, WAZ, height for age z-score (HAZ) as well as sex, age, and region, and  $d_{t,j}(\mathbf{L}_t)$  refer to dynamic treatment rules assigning treatment based on CD4 count and CD4%. The quantity of interest is cumulative mortality (under no censoring and loss to follow-up) after T months, that is  $\theta = \mathbb{P}(Y_{(\bar{a}^*,t)} = 1|\bar{C}_t = 0, \bar{M}_t = 0, \bar{Y}_{t-1} = 0)$ . We compare mortality estimates for several interventions  $d_t^*(\mathbf{L}_t^1, \mathbf{L}_t^2)$  such as: (i) immediate ART initiation irrespective of CD4 count and CD4%, (ii) assign ART if CD4 count < 750 cells/mm³ or CD4% < 25%, or (iii) assign ART if CD4 count < 350 cells/mm³ or CD4% < 15%.

Under the assumption of consistency (if  $\bar{\mathbf{A}}_{t,i} = \bar{\mathbf{a}}_{t,i}$ , then  $\mathbf{Y}_{(\bar{\mathbf{a}},t)} = \mathbf{Y}_t$  for  $\forall t, \bar{\mathbf{a}}$ ), no unmeasured confounding (conditional exchangeability,  $\mathbf{Y}_{(\bar{\mathbf{a}}^*,t)} \perp A_t | \bar{\mathbf{L}}_t, \bar{A}_{t-1}$  for  $\forall t, \bar{\mathbf{a}}$ ), and positivity  $(P(\bar{\mathbf{A}}_t = \bar{\mathbf{a}}_t | \bar{\mathbf{L}}_t = \mathbf{I}_t) > 0$  for  $\forall t, \bar{\mathbf{a}}, \mathbf{I}$ ), the g-computation formula can estimate cumulative mortality at time T (under the scenario of no loss to follow-up and no censoring) as

$$\sum_{t=1}^{T} \mathbb{P}(Y_{(\bar{a}^*,t)} = 1 | \bar{C}_t = 0, \bar{M}_t = 0, \bar{Y}_{t-1} = 0) =$$

$$\sum_{t=1}^{T} \int_{\bar{\mathbf{I}} \in \bar{\mathbf{L}}_t} \begin{cases} \mathbb{P}(Y_t = 1 | \bar{A}_t = \bar{a}_t^*, \bar{\mathbf{L}}_t = \bar{\mathbf{I}}_t, \bar{C}_t = 0, \bar{M}_t = 0, \bar{Y}_{t-1} = 0) \\ \prod_{t=1}^{T} \int_{\bar{\mathbf{I}} \in \bar{\mathbf{L}}_t} \mathbb{P}(Y_t = 1 | \bar{A}_{t-1} = \bar{a}_{t-1}^*, \bar{\mathbf{L}}_{t-1} = \bar{\mathbf{I}}_{t-1}, \bar{C}_t = \bar{M}_t = \bar{Y}_{t-1} = 0) \\ \times \mathbb{P}(Y_{t-1} = 0 | \bar{A}_{t-2} = \bar{a}_{t-1}^*, \bar{\mathbf{L}}_{t-2} = \bar{\mathbf{I}}_{t-2}, \bar{C}_{t-1} = 0) \\ \bar{M}_{t-1} = \bar{Y}_{t-2} = 0) \end{cases} d\bar{\mathbf{I}}$$
(A.1)

see Westreich et al. (2012) and Young et al. (2011) about more details and implications of the representation of the g-formula in this context. Note that for ordered  $\mathbf{L}_t = \{\mathbf{L}_t^1, \dots, \mathbf{L}_t^q\}$  the first part of the inner product of (A.1) can be written as

$$\prod_{t=1}^{T} \prod_{s=1}^{q} f(\mathbf{L}_{t}^{s} | \bar{\mathbf{A}}_{t-1} = \bar{\mathbf{a}}_{t-1}^{*}, \bar{\mathbf{L}}_{t-1} = \bar{\mathbf{I}}_{t-1}, \mathbf{L}_{t}^{1} = \mathbf{I}_{t}^{1}, \dots, L_{t}^{s-1} = l_{t}^{s-1}, \bar{C}_{t} = \bar{M}_{t} = 0).$$

There is no closed form solution to estimate (A.1), but  $\theta$  can be approximated by means of the following algorithm; Step 1: use additive linear and logistic regression models to estimate the conditional densities on the right hand side of (A.1), i.e. fit regression models for the outcome variables CD4 count, CD4%, WAZ, and death at t = 1, 3, ..., 36 using the available covariate history and model selection. Step 2: use the models fitted in step 1 to

stochastically generate  $\mathbf{L}_t$  and  $\mathbf{y}_t$  under a specific treatment rule. For example, for rule (ii), draw  $\mathbf{L}_1^1 = \sqrt{\text{CD4}} \text{ count}_1$  from a normal distribution related to the respective additive linear model from step 1 using the relevant covariate history data. Set  $A_1 = 1$  if the generated CD4 count at time 1 is  $< 750 \text{ cells/mm}^3$  or CD4% < 25%. Use the simulated covariate data and treatment as assigned by the rule to generate the full simulated dataset forward in time and evaluate cumulative mortality at the time point of interest. We refer the reader to Schomaker et al. (2016), Westreich et al. (2012), and Young et al. (2011) to learn more about the g-formula in this context.

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### 21

## BOOTSTRAP INFERENCE WHEN USING MULTIPLE IMPUTATION

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