Multiple imputation as an alternative method to simulate covariate distributions: comparison with joint multivariate normal and bootstrap techniques

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CONFLICT OF INTEREST

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Abstract

Clinical trial simulation (CTS) is a valuable tool in drug development. To obtain realistic scenarios, the subjects included in the CTS must be representative of the target population. Common ways of generating virtual subjects are based upon bootstrap (BS) procedures or multivariate normal distributions (MVND). Here, we investigated the performance of an alternative method based on multiple imputation (MI). Age, weight, serum creatinine, creatinine clearance, sex and race data from a hypertension drug development program were used. The methods were evaluated based on the original data set (internal evaluation) and on their ability to reproduce an older, unobserved population (extrapolation). Similar results were obtained in the internal evaluation in terms of summary statistics. However, BS was able to preserve the correlation structure of the empirical distribution, which was not adequately reproduced by MVND; MI was in between BS and MVND. BS does not allow to extrapolate to an unobserved population. Improved extrapolation performance of the continuous covariates was observed for MI over MVND, yet after removing the healthy subject data from the training data set, there was no clear difference between the methods. Sex was better predicted by MVND vs. MI, while similar results were obtained for race. If CTS is used to simulate within the range of the observed distribution, the BS is the preferred method for covariates simulation. When extrapolating to new populations, a parametric method like MI/MVND is needed. As MVND rests on relatively strong assumptions, MI appears to be more robust when deviations from these assumptions occur.

Introduction

In several research fields that aim to study complex systems, mathematical modeling is routinely used to quantitatively describe the system, generate or test hypotheses and explore system behavior by means of model simulations. Drug discovery and development is one such field, that has seen the application of modeling and simulation - or pharmacometrics - growing at a fast pace in the last decades [1]. Arguably, the success of pharmacometrics lies in its ability to integrate and synthesize evidence collected from heterogenous sources throughout the drug development spectrum, ultimately providing a sound quantitative input to the decision-making process in pharmaceutical R&D [2-4].

In the pharmacometrician's toolkit, clinical trial simulation (CTS) offers the possibility to mitigate the risk of study failure by prospectively exploring the performance of a given study design [5]. Among others, applications of CTS include proof-of-concept study design [6], outcome prediction in phase 3 [7], pediatric trial optimization [8,9], evaluation of non-adherence [10,11] and guidance in dose titration decisions [12]. CTS can be broken down into three building blocks: a disease model, a drug model and a trial model [13]. The trial model requires the definition of a patient population through a set of characteristics, often termed covariates; in order to obtain realistic simulation scenarios, the set of covariates included in the CTS must be representative of the target population.

Common ways of generating covariate distributions for CTS are based upon non-parametric bootstrap (BS) procedures or multivariate normal distributions (MVND) [14,15]. While BS is a non-parametric method, MVND requires certain parametric assumptions to be met by the original data set at hand. The different nature of these two methods brings respective pros and cons: with the BS it is not possible to extrapolate outside of the observed distribution, but it guarantees that the virtual

subjects will be physiologically realistic; conversely, extrapolation is enabled by the parametric trait of the MVND, but a price may have to be paid in terms of physiological plausibility.

Multiple imputation (MI) [16,17] is a technique used to handle complex missing data problems in statistical analysis, where multiple imputed data sets are analyzed separately, and inference is made on the pooled results. The alternative approach presented in this work rests on the theoretical ground of MI, but instead of using the underlying models to impute missingness, they are used to simulate completely new covariate data sets. Although the present work does not deal with imputations per se, the MI acronym is retained as the methodology underpinning the current analysis is largely inherited from the one developed for multiple imputation of missing data.

The objectives of this analysis were to investigate the operating characteristics of MI when used to simulate covariates distributions, and to compare them with those of BS and MVND.

Methods

Data

The data set used to build the simulations, hereafter referred to as the original data set, was obtained from a hypertension drug development program with data in 233 healthy subjects (HS) and 706 patients. The original data set contained the baseline values of the following covariates: age, weight (WT), serum creatinine (SCR), creatinine clearance (CRCL), sex and race. The summary statistics of the covariates in the original data set are reported in Table 1. The histograms of the continuous covariates stratified by HS vs. patients and the scatterplot matrix of the log-transformed continuous covariates are shown in Figure 1A and 1B, respectively.

Covariate simulation methods

BS. The BS method consisted of sampling, with replacement, covariate vectors from the original data set.

MVND. The MVND was implemented based on the framework presented in Tannenbaum et al. [15], that is briefly described. Before estimating the parameters of the MVND from the original data set, continuous covariates are log-transformed to constrain them to be positive; the covariate vectors simulated with the MVND are then exponentiated back to obtain the actual covariate values. As to categorical covariates, no pre-transformation is used, and they are treated as if they were continuous variables. This implies that the MVND can generate non-discrete values for categorical covariates, which then must be mapped back to their respective category based on a continuous critical value (see [15] for more details). Two important assumptions of the MVND are that the covariates in the original data set follow the same known distribution, and that they are linearly related to each other. A third assumption is that all the marginal distributions should not display clear multimodal trends. No truncation was applied to the covariates simulated with the MVND.

MI. MI was performed using the fully conditional specification (FCS) algorithm (also known as multivariate imputation by chained equations) as implemented in the R package *mice* version 3.6.0 [18]. FCS is an iterative method in which missing data are imputed on a variable-by-variable basis. The *mice* package offers the opportunity to choose from a selection of linear imputation models; here, the default methods were used, namely predictive mean matching (PMM) [19] and multinomial logistic regression for continuous and categorical covariates, respectively. PMM first calculates the predicted value of the target covariate according to the specified linear prediction model, secondly forms a set of donors/neighbors from the original data set constituted by the K closest values to the predicted one (K=5 in the present analysis), and finally makes the actual prediction by randomly drawing one value form the set of donors. Thus, the value of the simulated covariate will be contained in the original data set.

The MI simulations were performed as imputation of data sets where all covariates were assumed to be missing, leveraging the original data to train each univariate imputation (prediction) model (an illustrative example using a standard linear model is shown in Figure S1). An ad-hoc R function was developed and used to automate covariates simulation with MI (Supplementary Material 1).

Simulations set up and methods comparison

N=30 replicates of the same size as the original data set were simulated using BS, MVND and MI. CRCL was not directly simulated but derived from the simulated values of WT, SCR and sex using the Cockcroft-Gault [20] formula, similarly to what was done in the original data set.

In a first step, mean, standard deviation (SD), median, range and variance-covariance matrix for continuous covariates and proportions for categorical covariates were calculated for each of the 30 simulated replicates. Secondly, for each replicate *r*, the relative prediction error between the statistic

of the simulated data set ($P_{sim,r}$) and the original statistic (P_{org}) was computed as rPE_r (%) = ($P_{sim,r}$ - P_{org})/P_{org}*100. Finally, relative bias (rBias) and root mean squared error (rRMSE) were derived as $\frac{1}{N}\sum_{r=1}^{N} rPE_r$ and $\sqrt{\frac{1}{N}\sum_{r=1}^{N}(rPE_r)^2}$, respectively.

The comparisons described above were carried out under three different scenarios. Scenario A used the entire original data set to inform the BS, MVND and MI simulations (internal evaluation). In Scenario B, with the aim of investigating the extrapolation performance of the methods, the original data set was divided into a training and a test data set, where only the training data set was used to inform the simulations, while the test data set was used to assess the predictive performance of the methods (external evaluation). The training data set was defined as all subjects in the original data set younger than 55 years of age, mimicking a CTS exercise executed to investigate the features of a clinical trial performed in an older, unobserved population. Scenario C was the same as Scenario B but excluding HS data from the training data set. By definition, the BS does not allow to extrapolate outside of the empirical distribution, hence Scenarios B and C were tested for MI and MVND only. In Scenario B and C, the MVND simulations for age were obtained by truncating the distribution in the range 55-77 years. The age values simulated by the MVND were then used to seed the MI simulations (see example B in Supplementary Material 1). Accordingly, only the covariance terms for age were included in the evaluation, whereas the other statistics were not.

Results

Scenario A

Accuracy (rBias) and precision (rRMSE) of the continuous statistics are shown in Figure 2A-B. The mean and median of the original data set were maintained in the simulated population for all the methods. Likewise, SD and range were well estimated by BS and MI, whereas MVND resulted in larger rBias and rRMSE for the range of all covariates and for the SD of age. Figure 2C shows that the overall operating characteristics for the simulation of categorical covariates were similar across the three methods. BS was able to preserve the correlation structure of the empirical distribution, which was instead not adequately reproduced by MVND; MI was in between BS and MVND (Figure 3A). This in turn resulted in the lowest (BS) and highest (MVND) rBias and rRMSE in the elements of the variance-covariance matrix (Figure 3B-C).

Scenario B

Using MI for the simulation of an older patient population led to lower rBias and rRMSE in the summary statistics of the continuous covariates, compared to MVND (Figure 4A-B). Figure 4C shows that the prediction of the proportion of males and females in the extrapolated data set was more accurate and precise for MVND vs. MI, while similar performance was obtained for race.

Scenario C

When the HS data were removed from the training data set, no clear differences were observed between MI and MVND: some continuous covariates were better predicted by MVND (e.g. serum creatinine) and some others by MI (e.g. WT) (Figure 5A-B). As displayed in Figure 5C, sex was still more accurate and precise for MVND vs. MI.

Discussion

To maximize the predictability of a CTS exercise, plausible covariate values - representative of the target patient population - must be included in the trial model. Previous studies have investigated the operating characteristics of MVND as a tool to generate virtual populations [15], and compared them with BS methods [14]. In the present work, we introduced an alternative approach to covariate simulations that borrowed the methodology used for multiple imputation of incomplete data sets in statistical analysis [16,17]. In addition, we have also explored the extrapolation performance of the methods in predicting the summary statistics of an older, unobserved patient population.

In the internal evaluation (Scenario A) the three methods adequately reproduced the summary statistics of the continuous covariates present in the original data set (Figure 2A-B). The results indicated that, for some covariates like age and SCR, dispersion parameters were not very well predicted by MVND, which in turn led to the generation of implausible virtual subjects (e.g. 150 years old). Truncating the simulated covariates to more realistic values could help mitigating this problem; however, this was not assessed in the present analysis primarily because the cut-off values should be selected on a case-by-case basis, whereas the present work aimed at maximizing the generalizability of the results. In terms of categorical covariates, no clear differences between the operating characteristics of the three methods stood out; poorly represented categories, like “Other” and “American Indian” for race, were characterized by large rBias and rRMSE (Figure 2C).

Because the relationship between some pairs of log-transformed covariates deviated significantly from linearity (see e.g. age~WT correlation in Figure 1B), MVND provided more inaccurate and imprecise predictions of the covariance terms compared to BS and MI (Figure 3B-C). As expected, the BS could reproduce the original relationship between covariates regardless of its shape (Figure

3A), while MI appeared to be more robust than MVND with respect to deviation from the linearity assumptions.

In Scenario B, the aim was to evaluate the extrapolation capabilities of MVND and MI by assessing their predictive performance on a test data set composed by subjects older than 55 years of age, when the simulations were informed by a training data set from younger subjects. Similar to Scenario A, the results suggested that in general MI achieved higher accuracy and precision levels than MVND for continuous covariates (Figure 4A-B). While comparable performance was observed for the prediction of the race categories, biased and imprecise predictions of the proportions of males and females were obtained with MI. Although a previous study comparing MVND and MI approaches for multiple imputations found that MI is more accurate than MVND whenever the data include categorical variables [21], the simulations set up and aims of that study differed from those of the present work, and make it difficult to objectively compare the results.

When the HS data were removed from the training data set (Scenario C), the non-linearities in the correlation between age and other covariates were diminished (purple line in Figure 1B). As a result, the extrapolation performance of MVND improved in a remarkable fashion compared to Scenario B and, although the MI operating characteristics also improved, no large differences were observed between the two methods in terms of continuous covariates (Figure 4A-B). rBias and rRMSE for sex were still lower for MVND vs. MI.

In general, MI appeared to be more robust to departures of the data from normality assumptions. The reason seems to lie more on the PMM method used to predict the new covariate value rather than in the different statistical background between the two methods (in MVND the data are modeled as a sample from a joint multivariate normal distribution whereas in MI each variable is modeled

conditionally on all the others). In fact, PMM slightly downweighs the model prediction by picking up a covariate value in the original data set that is very close to the predicted one; nevertheless, it should be noted that if strong non-linear relations exist in the original data set, the consequent misspecification in the underlying predictive model could result in poor MI performance [22]. Tannenbaum et al [15] suggest to carry out additional methods prior to creating the MVND in order to correct for non-linear relations between continuous covariates, but this was not performed in the present implementation (apart from log-transformation). Although this could have improved the MVND results, especially in terms of the variance-covariance matrix, it is likely that MI would have also benefitted from such pre-transformations given that it is still based on linear prediction models. Likewise, truncation of MVND simulations to plausible values might also have positively impacted the MVND operating characteristics. On the other hand, it can be noted that while MI simulates ready-to-use covariates (Supplementary Material 1), MVND can in certain instances require additional post-processing of its input as well as output data, which in turn requires extra efforts and further assumptions to be made.

The different results of the MVND between Scenario B and C can be attributed primarily to the distribution of age in HS, which is approximately uniform between 18 and 45 years. As shown in Figure 1A, the HS data distort the overall distribution of age, which is instead well approximated by a normal distribution in patients alone. Presumably, this is also the reason for the MVND issues in reproducing dispersion metrics under Scenario A. This suggests that study-specific nuisance covariates, such as HS vs. patients, should be handled carefully before embarking in a CTS effort.

BS was excluded from Scenario B and C because, by definition, it does not allow to extrapolate outside of the empirical distribution. This limitation can be overcome if observational data on the target indication are available, for example from databases based on routine clinical care used to

identify patients for enrollment in clinical trials. However, while for common indications like hypertension this might easily be achieved, large patient registries for less frequent diseases are often not available.

MI performed with the *mice* package requires the specification of some options such as the number of donors K or the type of prediction model to use. All the defaults options were used in this analysis, yet the sensitivity of the results to the options choice should be further investigated. An interesting feature of *mice* that was not explored in the present work is that it potentially enables simulation of time-varying covariates, which cannot be done with an MVND approach. Furthermore, extrapolation to other clinical contexts and generalizability of the results obtained in this work should be further explored.

The simulation of covariates, together with a disease and a drug model, represent the minimum working components that enable the generation of an in-silico response to treatment of a group of patients. Thus, besides providing a tool for prospective investigations of study design features, CTS represents an appealing methodology for the creation of synthetic controls in clinical trials. Synthetic controls are formally defined as statistical methods that can be used to evaluate the comparative effectiveness of an intervention using external control data [23]. Although synthetic controls are usually based on collected real evidence [24], the use of predictive statistical models to simulate virtual responses to standard-of-care treatments has recently been proposed as a way to generate synthetic controls [25]. In the case of rare diseases and small populations in general (e.g. pediatrics) the use of control groups is often hampered by feasibility and ethical hurdles, simulated synthetic controls represent a promising alternative, as also indicated by their increased regulatory acceptance [26].

To conclude, the present analysis revealed that, if CTS is used to simulate within the range of the observed distribution (e.g. when studies in the target population are already available from other sources), the BS is likely the preferred method for covariates simulation, particularly because it is able to guarantee the physiological plausibility of the simulated covariates. Alternatively, when the CTS objectives involve extrapolations to new populations, a parametric method like MI or MVND is needed. As the MVND approach rests on relatively strong assumptions, i.e. linearly related covariates and unimodal distributions, MI appears to be more robust when deviations from these assumptions occur in the original data set used to inform the extrapolation.

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AUTHOR CONTRIBUTIONS

G.S. and E.N.J. wrote the manuscript; E.N.J. designed the research; G.S. and E.N.J. performed the research; G.S. analyzed the data.

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Figures

Figure 1. Histograms of continuous covariates colored by patients vs. healthy subjects (A) and correlation between pairs of continuous covariates (B). The solid line is a loess regressor.

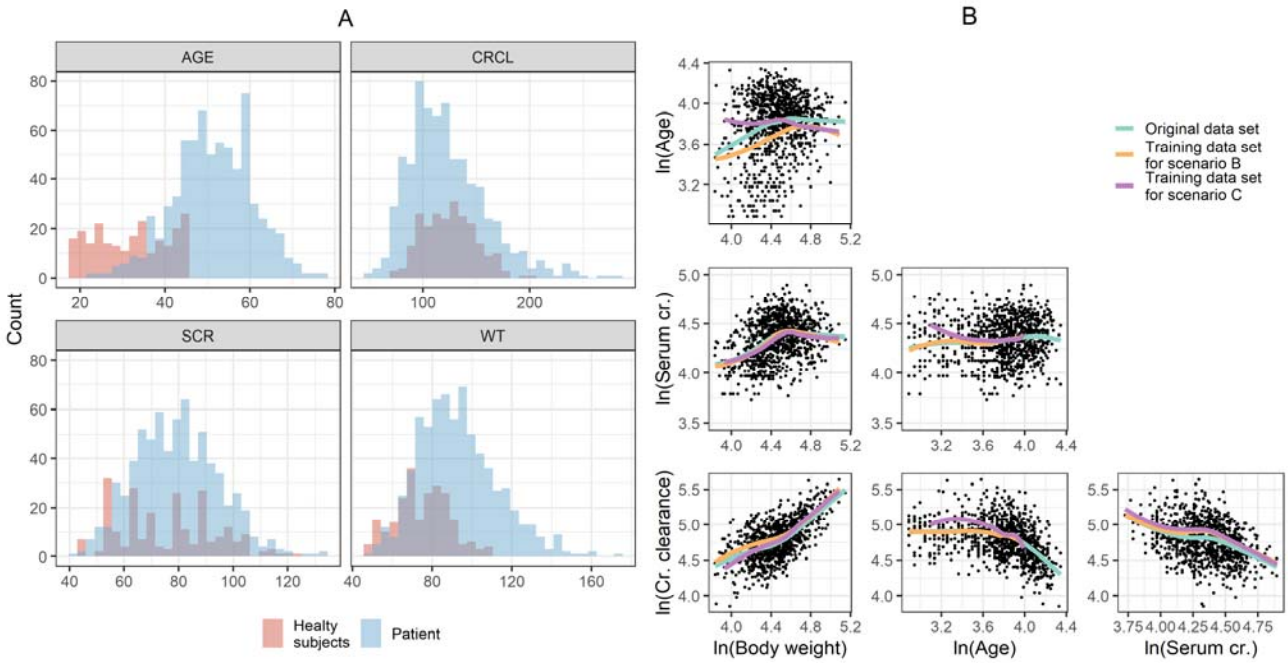


Figure 2. Relative Bias and RMSE for summary statistics of continuous (A and B) and categorical (C) covariates in Scenario A (cells where the absolute value of relative Bias/RMSE is greater than 30% are grayed out).

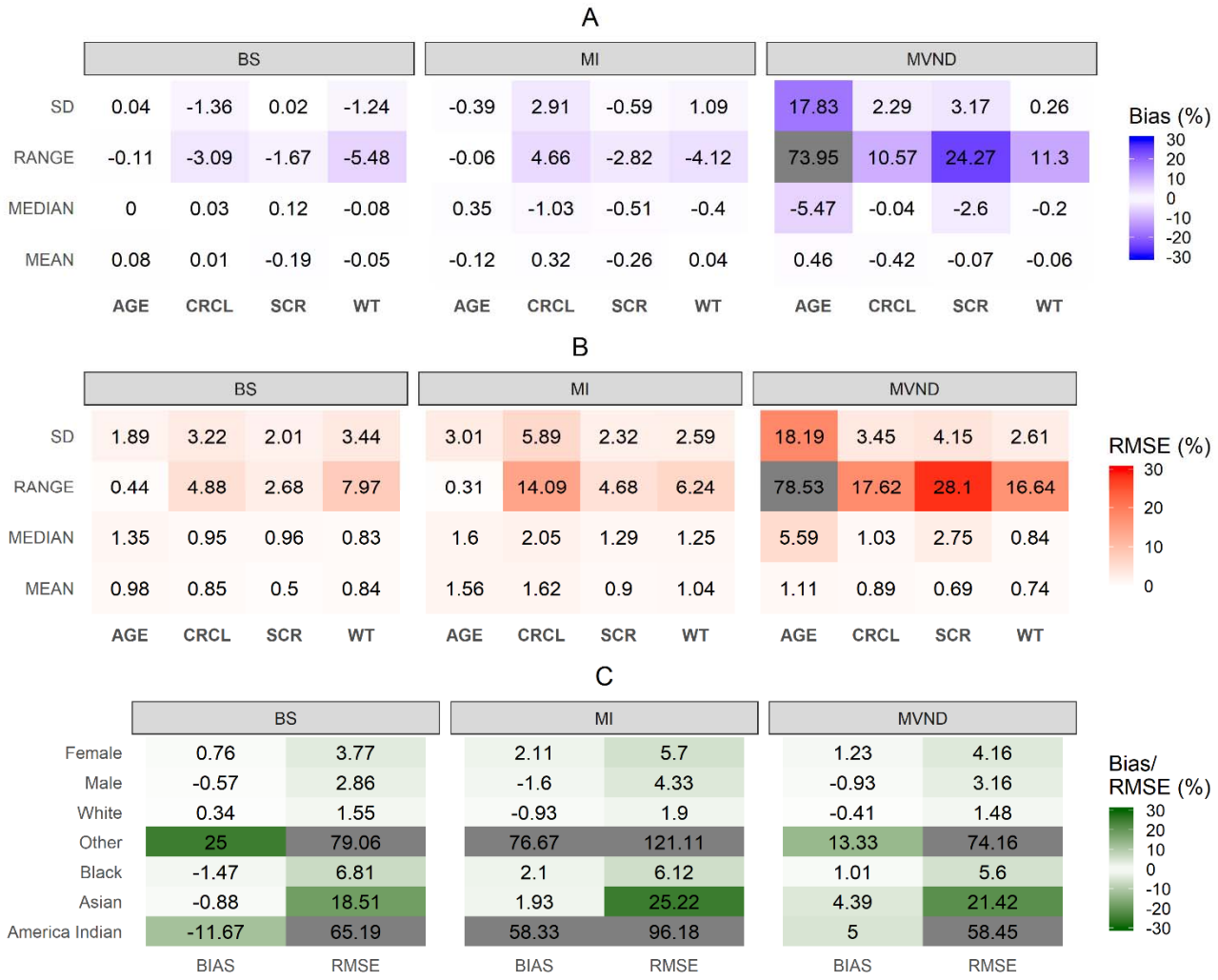


Figure 3. Visual predictive check of the relationship between pairs of continuous covariates (A): the black line represents a loess regressor through the original data set, while the shaded area depicts the 80% confidence iterval of the loess regressor fitted to each of the 30 replicates. Relative Bias (B) and RMSE (C) for the variance-covariance matrix of the continuous covariates (cells where the absolute value of relative Bias/RMSE is greater than 30% are grayed out). Scenario A.

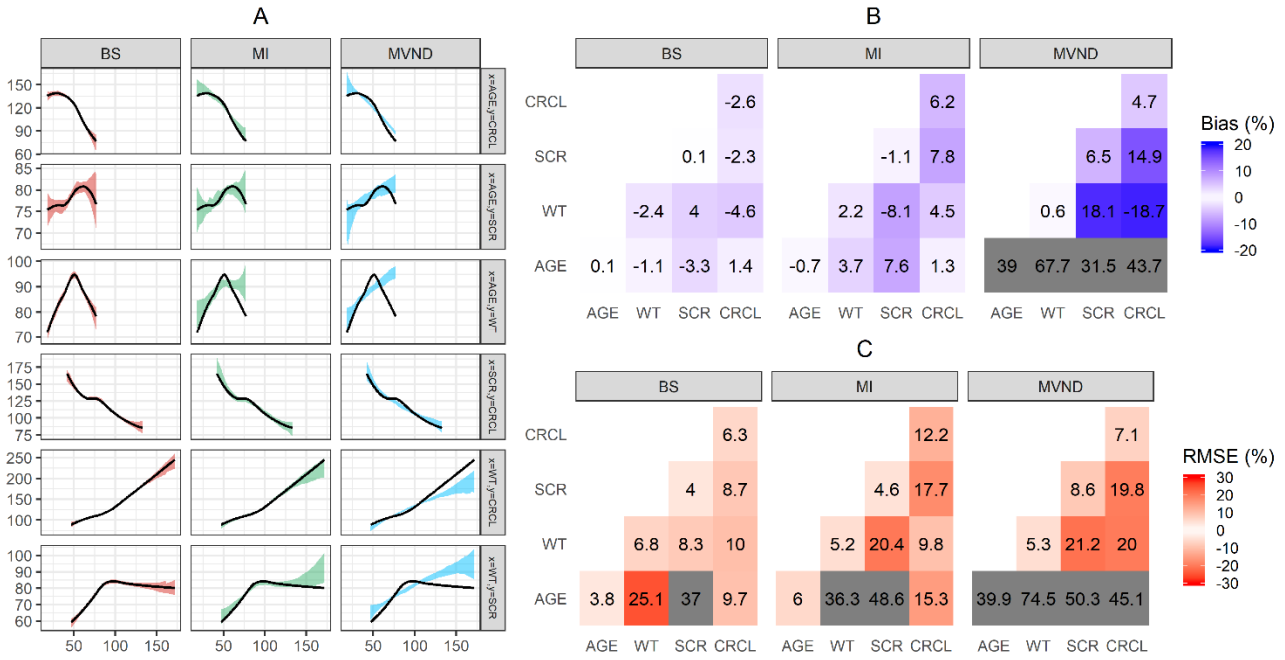


Figure 4. Relative Bias and RMSE for summary statistics of continuous (A) and categorical (C) covariates in Scenario B (cells where the absolute value of relative Bias/RMSE is greater than 30% are grayed out). Relative Bias and RMSE for the variance-covariance matrix of the continuous covariates (B) in Scenario B (cells where the absolute value of relative Bias/RMSE is greater than 100% are grayed out). There were no subjects with “race = other” in the training data set, therefore in subfigure C rBias and rRMSE were computed using the absolute difference instead of the relative one for this category.

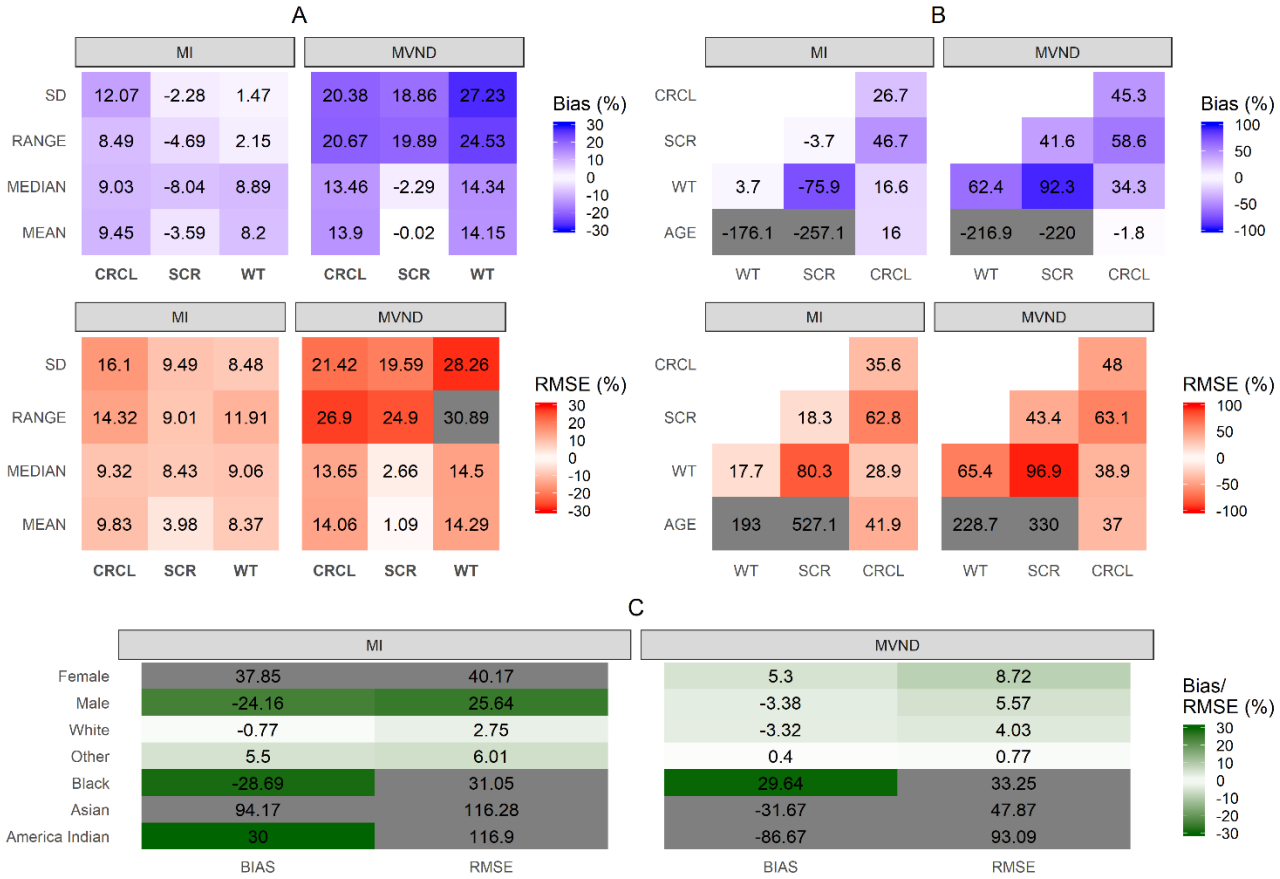


Figure 5. Relative Bias and RMSE for summary statistics of continuous (A) and categorical (B) covariates in Scenario C (cells where the absolute value of relative Bias/RMSE is greater than 30% are grayed out). Relative Bias and RMSE for the variance-covariance matrix of the continuous covariates in Scenario C (cells where the absolute value of relative Bias/RMSE is greater than 100% are grayed out).

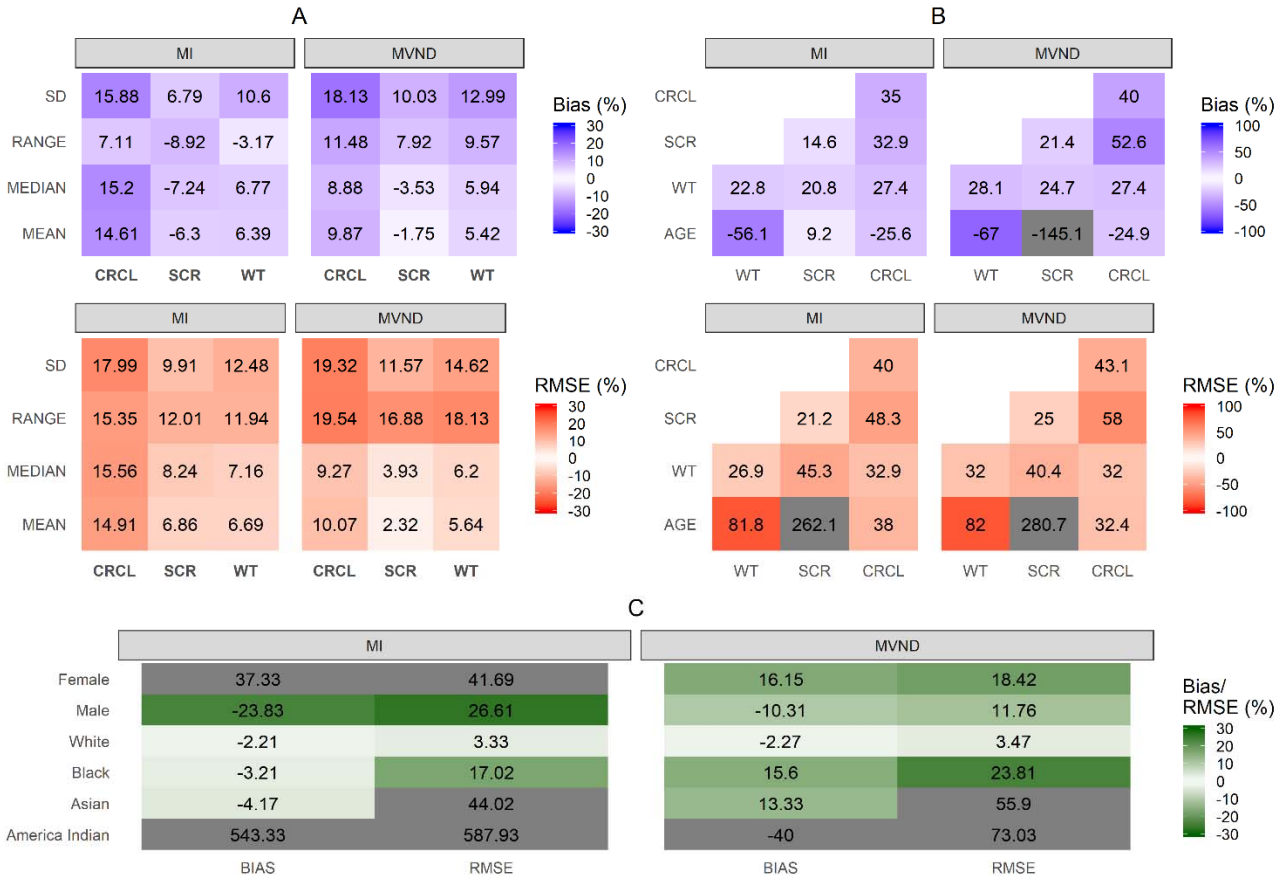
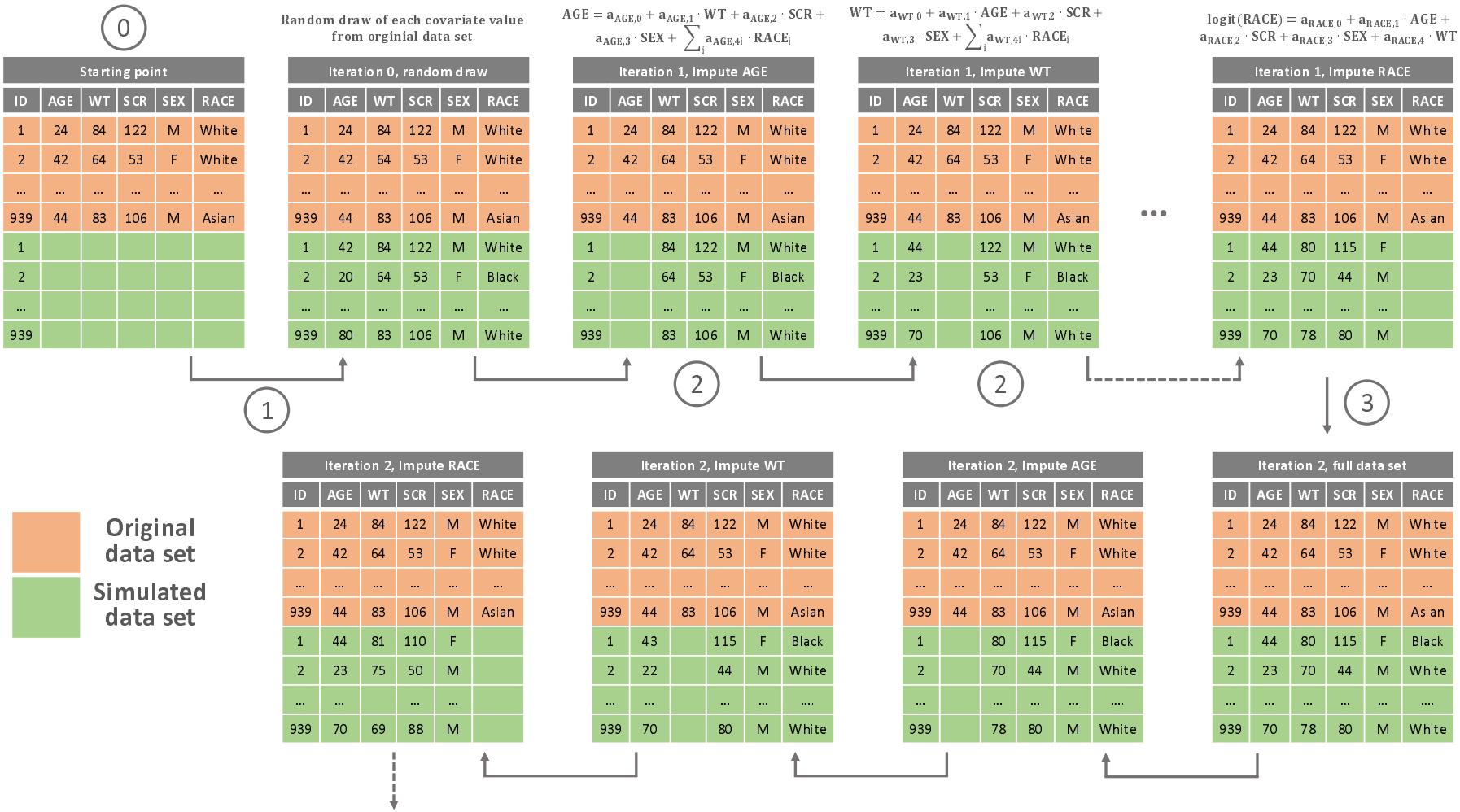


Figure S1. Illustrative example of the methodology used to simulate covariates with MI, using a standard linear model instead of predictive mean matching. The starting point is represented by a dummy data set with the same rows as the original data set and all covariates assumed to be missing, which is attached to the original data set (0). At iteration 0 all the missing data are first imputed by drawing a random sample from the original data set (1). During iteration 1, missing covariates are sequentially imputed: the covariate under question is modeled conditionally on all the others and the model prediction is used as imputation (2). When all the covariates have been imputed with the respective imputation model, a new full data set is obtained (3), which is then used as starting point for iteration 2. This iterative process goes on until convergence is reached, defined as the mean and standard deviation of each covariate being stable over the last iterations.


0
Random draw of each covariate value from orginial data set
$AGE = a_{AGE,0} + a_{AGE,1} \cdot WT + a_{AGE,2} \cdot SCR + a_{AGE,3} \cdot SEX + \sum_i a_{AGE,4i} \cdot RACE_i$
$WT = a_{WT,0} + a_{WT,1} \cdot AGE + a_{WT,2} \cdot SCR + a_{WT,3} \cdot SEX + \sum_i a_{WT,4i} \cdot RACE_i$
$logit(RACE) = a_{RACE,0} + a_{RACE,1} \cdot AGE + a_{RACE,2} \cdot SCR + a_{RACE,3} \cdot SEX + a_{RACE,4} \cdot WT$
Starting point
Iteration 0, random draw
Iteration 1, Impute AGE
Iteration 1, Impute WT
Iteration 1, Impute RACE
1
2
2
3
Iteration 2, Impute RACE
Iteration 2, Impute WT
Iteration 2, Impute AGE
Iteration 2, full data set
Original data set
Simulated data set

Tables

Table 1. Summary statistics of the covariates in the original data set.

Total number of subjects	939
Continuous covariates	
Age (years)	
Mean	46.4
SD	12.4
Median	47.0
Range	18.0-77.0
Weight (kg)	
Mean	88.5
SD	20.1
Median	86.6
Range	46.3-172
Serum creatinine (µmol/L)	
Mean	78.5
SD	16.2
Median	78.7
Range	41.5-133
Creatinine clearance (mL/min)	
Mean	124
SD	34.3
Median	120
Range	47.0-282
Categorical covariates	
Population, n (%)	
Patients	706 (75.2)
Healthy subjects	233 (24.8)
Sex, n (%)	
Males	534 (56.9)
Females	405 (43.1)
Race, n (%)	
White	737 (78.5)
Black	179 (19.1)
Asian	19 (2.0)
American Indian	2 (0.2)
Other	2 (0.2)

Supplementary Material 1

```
##-----------------------------------------------------------------------------------
##        File name: simCovMICE.R
##        Created: 2020-04-21
##        Use: function creating covariates distribution using mice
##
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##-----------------------------------------------------------------------------------

simCovMICE <- function(m = 5,
                       orgCovs,
                       catCovs = c("SEX","RACE"),
                       seedCovs = NULL,
                       targetRangeSeedCovs = NULL,
                       seedCovsValues = NULL,
                       nsubj = nrow(orgCovs),
                       contMeth = "pmm",
                       sampleFromReal = T,
                       ...)
  #####
## INPUTS:
##    m        --> how many replicates of the original data to generate
##    orgCovs  --> dataframe containing the original, observed, time-invariant covariates (ID should
not be included) that will be used to inform the imputation
##    catCovs  --> character vector containing the name of the categorical covariates in orgCovs
##    seedCovs --> character vector containing the name of the covariates that should be used to seed
the imputation, they will be sampled from the original data set
##    targetRangeSeedCovs --> if the seeding is based on a desired range, then define it here
##    seedCovsValues --> vector containing the seeding cov values
##    nsubj   --> number of simulated subjects, default is subjects in original data
##    contMeth   --> method used to predict continuous covariates within mice
##    sampleFromReal --> should seedCovs be sampled from orgCovs?
##    ... --> additional input to mice call
##
## OUPUT: a data frame with the simulated covariates
##
## NOTES: missing values in orgCovs must be coded as NA
#####
{
  library(tidyverse)

  # names of continuous covariates
  contCovs <- setdiff(names(orgCovs),catCovs)

  # create copy of the original data set with factor version of cat covs
  orgCovsF <- orgCovs %>% mutate_at(catCovs,function(x) as.factor(x))
```

```
  ## find covariates with missing values
  missVars <- names(orgCovs)[colSums(is.na(orgCovs)) > 0]

  # impute missing data once with mice
  if(length(missVars)>0)
  {
    imp1 <- mice::mice(orgCovsF, m=1, printFlag=FALSE, maxit = 15)
    orgCovs <- mice::complete(imp1)
  }

  miCovs <- orgCovs[1:nsubj,] %>% mutate_all(function(x) NA)


  if(!is.null(seedCovs))
  {
    if(sampleFromReal)
    {
      ## create vector of seedCov values contained in original data set
      poolSeed <-  orgCovs[orgCovs[,seedCovs]>=min(targetRangeSeedCovs) &
orgCovs[,seedCovs]<=max(targetRangeSeedCovs),seedCovs]
      ## do the actual sampling
      miCovs[seedCovs] <- sample(poolSeed,nsubj,replace = T)
    }
    else
      miCovs[seedCovs] <-  seedCovsValues
  }

  combCovs <- orgCovs %>% mutate(Type="Original") %>%
    bind_rows(miCovs %>% mutate(Type="Simulated")) %>%
    mutate_at(catCovs,function(x) as.factor(x))

  myPredMat <- mice::make.predictorMatrix(combCovs)
  myPredMat[,c("Type")] <- 0

  myMethods <- mice::make.method(combCovs)
  myMethods[contCovs] <- contMeth

  imp2 <-mice::mice(combCovs, m=m,printFlag=FALSE,predictorMatrix = myPredMat, method =
myMethods, ...)

  impCovs <- mice::complete(imp2,action="long") %>%
    filter(Type=="Simulated") %>%
    mutate(NSIM=.imp) %>%
    select(everything(),-.id,-Type,-.imp)

  return(impCovs)
```

```
}



##-------------------------------------------------------------------------------------
##
##      MINIMUM WORKING EXAMPLE ON THE USE OF simCovMICE()
##
##-------------------------------------------------------------------------------------

# A) Simulations without seeding

orgCovsEx <- data.frame(AGE = c(50,42,39,70),
                        WT  = c(84,64,88,55),
                        SMOKE = c(1,2,2,1))

myCovSimMICE1 <- simCovMICE(m = 2,orgCovs = orgCovsEx,catCovs = c("SMOKE"))
myCovSimMICE1

# B) Simulations using AGE as a seeding covariate: AGE is assumed to be
#    known, and sampled from the original data set, using only values within 40 and 50 years.

myCovSimMICE2 <- simCovMICE(m = 2,orgCovs = orgCovsEx,catCovs = c("SMOKE"),seedCovs
= "AGE", sampleFromReal = T,targetRangeSeedCovs = c(40,50))

myCovSimMICE2
```