smdi: An R package to perform structural missing data investigations on partially observed confounders in real-world databases

**Authors**: Janick Weberpals1, Sudha R. Raman2, Pamela A. Shaw3, Hana Lee4, Bradley G. Hammill2, Sengwee Toh5, John G. Connolly5, Kimberly J. Dandreo5, Fang Tian4, Wei Liu4, Jie Li4, José J. Hernández-Muñoz4, Robert J. Glynn1, Rishi J. Desai1

Author affiliations:

1Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

2Department of Population Health Sciences, Duke University School of Medicine, Durham, NC

3Biostatistics Division, Kaiser Permanente Washington Health Research Institute, Seattle, WA

4Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

5Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

**Correspondence:**

Janick Weberpals, RPh, PhD

Division of Pharmacoepidemiology and Pharmacoeconomics,

Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School,

1620 Tremont Street, Suite 3030-R, Boston, MA 02120, USA

Phone: 617-278-0932

Fax: 617-232-8602

Email: [jweberpals@bwh.harvard.edu](mailto:jweberpals@bwh.harvard.edu)

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# Abstract

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| Highlights |
| * … |

# Background

Electronic health records (EHR) are increasingly used to conduct real-world evidence (RWE) studies to complement evidence coming from randomized controlled trials (RCTs) [1,2]. Due to their detailed capture of clinical parameters such as vital signs, lab measurements, physician assessments and lifestyle factors, EHRs can significantly improve the ability to control for confounding and imbalances in prognostic factors between treatment groups, especially when linked to administrative claims databases [3]. However, such prognostic factors are often just partially observed which challenges the statistical analysis of the data and can result in severe bias when predicting or estimating treatment effects if not handled appropriately [4–6].

In order to make an informed decision about the most appropriate analytic approach to arrive at unbiased estimates, it is crucial to investigate and understand the potential patterns and mechanisms that underlie the partially observed confounder data [7–9]. Usually these are not known for a given RWE study but general guidance papers and frameworks have suggested various routine diagnostics to investigate missing data patterns and mechanisms (see definitions box). These methods comprise standard procedures such as comparing distributions of baseline characteristics and outcomes between patients with and without the partially observed covariate(s) [10–14], checking the ability to predict missingness based on observed data [11] and assessing if causal relationships between variables and their missingness are recoverable based on available data [15] guided by directed acyclic graphs [16,17] or M-graphs [18]. However, these methods have so far been only described and tested in isolation from each other and no principled approach exists. In addition, the practical implementation of all of these diagnostics is time-consuming, tedious and is consequently not often performed in both RWE and RCTs [19–21].

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| Definitions: Basic missing data taxonomies. |
| Patterns (taken from Van Buuren [7])  * Monotone pattern: If Yj is the jth column in a dataset *Y*, a missing data pattern is said to be *monotone* if the variables Yj can be ordered such that if Yj is missing then all variables Yk with *k > j* are also missing. This can occur, for example, in longitudinal studies with drop-out or with clinical labs which are typically measured together as part of a lab panel (e.g., renal or liver panel). * Non-monotone pattern: If the pattern is not monotone, it is called *non-monotone* or *general*.  Mechanisms (taken from Sondhi and Weberpals et al. [11])  * **MCAR**: The missingness does not depend on any other observed or unobserved covariate(s). * **MCAR**: The missingness depends and can be explained by other observed covariates. * **MNAR**: The missingness depends on unoberserved covariate(s). For example, the missingness may be explained by other covariate(s) which is/are not observed in the underlying dataset (MNARunmeasured). The missingness can also just dependent on the actual value of the partially observed covariate itself (MNARvalue). |

To overcome these shortcomings, we [22] have recently developed and evaluated a principled approach combining a range of missing data diagnostics in an US EHR-claims database linkage [23]. The results of this large-scale study revealed that the combination of these diagnostics characterized simulated missing data mechanisms well and provided helpful insights for the appropriate choice of analytic methods to handle the partially observed confounder data (e.g., missing data imputation).

To streamline and ease the implementation of these routine missing data diagnostics for confounder data in RWE studies, we here present and demonstrate the use of the smdi (structural missing data investigations) R package [24]. To that end, we first provide an overview on the package’s main functions including the underlying theoretical assumptions. We then demonstrate the practical application of the package by illustrating and end-to-end workflow with a hypothetical RWE study using a simulated oncology EHR dataset that comes bundled with the package.

# Methods

## Problem Formalization

As opposed to clinical trials, which are designed to collect data for research purposes in a harmonized manner, real-world data (RWD) are typically generated for administrative purposes (e.g., health insurance claims for billing purposes) or clinical documentation (e.g., EHR). Hence, confounders and prognostic factors, which need to be balanced between treatment groups in RWE studies, are usually not available for all patients at all necessary time points [25]. If the underlying mechanism for the missingness of such covariates is not at random, e.g., patients with higher levels of a prognostic biomarker are more likely to be missing, this can lead to bias in the resulting effect estimates for the studied treatments under common missing data approaches like complete case analysis or imputation [6]. Hence, it is of utmost importance to investigate the potential patterns and mechanisms to know if assumptions for specific missing data approaches hold [14,26].

## Theoretical Background and Main Package Functions

For the implementation of these routine missing data diagnostics, we categorized the main functions of the smdi R package into three group diagnostics based on their general analytic properties (**Table 1**). In this section, we will explain the basic ideas behind the main package functions, the parameters a user can specify, the results that are being returned by calling the functions and the interpretation of results. Generally, for all functions in the smdi package, a *dataframe* is expected (data parameter) as input with a format where one row represents one unqiue patient and the columns stand for the variables relevant for the study, i.e., the exposure, outcome, fully observed covariates and the partially observed covariates (one-row-per-patient format). Any non-informative columns, such as patient identifiers, date columns or zip codes should be dropped from the dataframe before calling the functions. Throughout all functions, the user has the option to specify a vector with the column name(s) of the partially observed covariate(s) that should be investigated (covar parameter). If nothing is specified, all functions consider automatically any variable in the dataframe that exhibits at least one missing value.

### Group 1 Diagnostics

The aim of the smdi\_asmd(), smdi\_hotelling() and smdi\_little() functions is to explore dissimilarities in patient characteristics between those with and without observed values for the partially observed covariate. According to Rubin’s framework on inference and missing data [8], when missingness is at random (MAR), it can be explained by observed covariates. Consequently, significant differences in patient characteristics would be expected under a MAR mechanism between strata of patients with and without the partially observed covariate. If the missingness depends only on unobserved factors (missing not at random [MNAR]) or does not depend on either observed or unobserved covariates (missing completely at random [MCAR]), differences should not be observable.

To quantify and test such differences, the smdi\_asmd() function computes absolute standardized mean differences (ASMD) of observed patient characteristics [27–29]. The function returns an *asmd* object which displays an aggregated summary of the average or median ASMDs (which can be flexibly chosen using the median parameter) along with corresponding minimum and maximum AMSDs observed. The *asmd* object also returns a detailed ‘Table 1’ for each partially observed covariate displaying the distributions of observed patient characteristics and resulting ASMDs between patients with and without an observed value for the partially observed covariate. For a graphical visualization of this, the function also creates a *ggplot2* graph [30] illustrating the ASMDs for each compared patient characteristic in descending order.

The smdi\_hotelling() and smdi\_little() functions complement the smdi\_asmd() function by examining the differences in patient characteristics as a formal statistical hypothesis test. Hotelling’s test [12,31] formalizes this is a multivariate t-test for each partially observed covariate, which means that smdi\_hotelling() returns a test statistic and a corresponding p-value for each each partially observed covariate individually. In contrast, Little’s test [13,32] (smdi\_little()) computes a single global chi-square test statistic and p-value across all partially observed covariates with the null hypothesis that the data is MCAR.

### Group 2 Diagnostics

The group 2 diagnostics assesses the ability to predict missingness based on observed covariates via the smdi\_rf() functions. This function trains and fits a random forest classification model [11,33] to predict the missing indicator of the partially observed covariate given observed covariates as the predictors. If the resulting area under the receiver operating characteristic curve (AUC) is meaningfully higher than 0.5, this would give some evidence for MAR being the underlying missingness mechanism. In case of values close 0.5, this would rather indicate a random prediction and translate to potential MCAR or MNAR mechanisms.

The function returns an object of class rf which generically displays an overview of the AUC values of all partially observed covariates. The AUC values are based on the prediction made in the respective test datasets. For more details, the rf object additionally includes a *ggplot2* graph for each partially observed covariate displaying the relative importance of the predictors in the training dataset expressed as the mean decrease in accuracy. This metric can be valuable for interpreting and identifying strong predictors of missingness. It quantifies how much the accuracy of the prediction (i.e., the ratio of correct predictions to the total number of predictions made) would decrease if we excluded a specific predictor from the prediction model. For tuning the random forest model, the smdi\_rf() function has a few parameters that can be specified by the user for optimization such as the number of trees to grow (ntree; default is 1,000 trees), the ratio of the split between train and test datasets (train\_test\_ratio; default is a 70/30 split) and the number of cores to parallelize the computation on (n\_cores, default is 1) [34], since this function can be very time consuming, especially with larger datasets.

### Group 3 Diagnostics

Finally, the third group diagnostics with the smdi\_outcome() function examines the association of the missingness indicator of the partially observed covariate and the outcome under study. The function will compute both a univariate model and a model adjusted for all other covariates included in the dataset. In previous simulations, we observed characteristic patterns for univariate and adjusted associations of the missing indicator and the outcome that matched simulated underlying missingness mechanisms [23]. As one would expect, under a MCAR mechanism there was no difference in the outcome between patients with and without a value for the partially observed covariate. Under MAR, given that missingness can be explained by observed covariates, a potential spurious association in the univariate model disappeared after adjustment. If the missingness followed any MNAR mechanism, an association was observed in both univariate and adjusted models.

Currently, smdi\_outcome() supports three outcome regression types: linear regression (*lm* [35]) for continuous outcomes, logistic regression (*glm* [35]) for binary outcomes and a Cox proportional hazards model (*coxph* [36]) for time-to-event outcomes. Besides the specification of the regression type, the user needs to specify the name of the column that contains the outcome using the *form\_lhs* parameter (e.g., Surv(eventtime, status) in case of a Cox model) and if resulting beta coefficients should be exponentiated or not. The function returns a table with univariate and adjusted beta coefficients and 95% confidence intervals for each partially observed covariate.

## Exemplary RWE Study and Data Generation

### Study Population

To showcase the practical implementation and suggested workflow when working with smdi, the package comes with a *de novo* simulated example EHR dataset that mimics a new-user cohort of 2,500 lung cancer patients initiating two comparable antineoplastic drug treatment regimens. The aim of the exemplary RWE study is to compare the comparative effectiveness of these two drug regimens in presence of confounding and three partially observed covariates, each following a different missingness mechanism. An overview of the dataset and baseline patient characteristics are provided in **Table 2**.

### Simulation Design

The data generation process is described in detail in the Supplementary Methods. In brief, for this exemplary RWE study, we simulated a binary exposure (*Drug A versus Drug B*), a time-to-event outcome (*overall survival,* defined *as* as the time from treatment initiation until all-cause mortality or censoring) and 11 covariates, seven of which were true confounders (i.e., associated with both exposure and outcome), two were prognostic factors (i.e., associated only with the outcome but not with exposure) and two covariates which were neither associated with the exposure nor the outcome (**Table 3**). We generated the survival times for the outcome assuming parametric event times following an exponential distribution and a truncated follow-up time of 5 years (Supplementary Table and Supplementary Figure ) [37]. The desired true treatment effect estimate was defined with a hazard ratio (HR) of 1.0. The strength of association between each covariate and the exposure and the outcome is displayed in Supplementary Table x and y, respectively.

### Missingness generation

To simulate missingness

# Results

# Discussion

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# Tables

Table 1: Overview of the main functions in smdi to characterize potential underlying missingness mechanisms.

| **Function** | **Description** | **Generic S3 print() output** | **Object output** | **Interpretation** |
| --- | --- | --- | --- | --- |
| Group 1 Diagnostics - Comparing the distribution of observed covariates between patients with versus without a value for the partially observed covariate | | | | |
| **smdi\_asmd()** | Computes the absolute standardized mean differences (ASMD) of patient characteristics between patients with versus without a value for the partially observed covariate(s) | Aggregated summary table of the average/median and minimum/maximum ASMD range for all specified partially observed covariates | - Detailed *Table 1* illustrating distributions and individual ASMD for each compared patient characteristic  - ggplot2 graph illustrating the individual ASMD for each compared patient characteristic in descending order  - Aggregate summary of the average/median and minimum/maximum ASMD range for the selected partially observed covariate | - ASMD < 0.1: no imbalances in observed patient characteristics; missingness may be likely completely at random or not at random (~MCAR, ~MNAR)  - ASMD > 0.1: imbalances in observed patient characteristics; missingness may be likely at random (~MAR) |
| **smdi\_hotelling()** | Computes Hotelling's multivariate t-test for each partially observed covariate, examining patient differences conditional on having an observed covariate value or not. | Aggregated summary table of the Hotelling's test p-values for all specified partially observed covariates | Detailed Hotelling test statistics | High test statistics and low p-values indicate differences in baseline covariate distributions and null hypothesis would be rejected (~MAR) |
| **smdi\_little()** | Computes a single global chi-square test statistic across all partially observed covariates with a null hypothesis that the data is missing completely at random. | Detailed Little's test statistics | Detailed Little's test statistics | High test statistics and low p-values indicate differences in baseline covariate distributions and null hypothesis would be rejected (~MAR) |
| Group 2 Diagnostics - Assessing the ability to predict missingness based on observed covariates | | | | |
| **smdi\_rf()** | Trains and fits a random forest classification model to assess the ability to predict missingness indicator for the partially observed covariate(s). | Aggregated summary table with the area under the receiver operating characteristic curve (AUC) value for each partially observed covariate | - Individual AUC value  - ggplot2 figure illustrating the variable importance for the prediction made expressed by the mean decrease in accuracy per predictor | - AUC values ~ 0.5 indicate completely random or not at random prediction (~MCAR, ~MNAR)  - Values meaningfully above 0.5 indicate stronger relationships between covariates and missingness (~MAR) |
| Group 3 Diagnostics - Evaluates whether missingness of a covariate is associated with the outcome | | | | |
| **smdi\_outcome()** | Fits outcome model (linear, logistic or proportional hazards depending on the outcome under study) with the missingness indicator of the partially observed covariate(s). The estimates are computed both as a univariate model (just considering the missingness indicator) and an adjusted model with all covariates in the dataset. | Aggregated summary table with the univariate and adjusted estimate for each partially observed covariate | Aggregated summary table with the univariate and adjusted estimate for each partially observed covariate | - No association in either univariate or adjusted model and no meaningful difference in the log HR after full adjustment (~MCAR).  - Association in univariate but not fully adjusted model (~MAR).  - Meaningful difference in the log HR also after full adjustment (~MNAR). |

Table 2: Patient characteristics of the exemplary cohort used to showcase the smdi package.

| **Characteristic** | **Overall**, N = 2,5001 | **Drug A**, N = 1,5021 | **Drug B**, N = 9981 | **p-value**2 |
| --- | --- | --- | --- | --- |
| Age (years) | 61 (51, 70) | 63 (54, 73) | 57 (48, 66) | <0.001 |
| Female | 922 (37%) | 588 (39%) | 334 (33%) | 0.004 |
| Smoking history | 1,253 (50%) | 686 (46%) | 567 (57%) | <0.001 |
| Physically active | 882 (35%) | 502 (33%) | 380 (38%) | 0.017 |
| ALK status | 69 (2.8%) | 39 (2.6%) | 30 (3.0%) | 0.5 |
| Tumor histology | 508 (20%) | 288 (19%) | 220 (22%) | 0.081 |
| Socio-economic status |  |  |  | 0.4 |
| 1\_low | 524 (21%) | 302 (20%) | 222 (22%) |  |
| 2\_middle | 969 (39%) | 592 (39%) | 377 (38%) |  |
| 3\_high | 1,007 (40%) | 608 (40%) | 399 (40%) |  |
| History of COPD | 1,338 (54%) | 738 (49%) | 600 (60%) | <0.001 |
| ECOG score |  |  |  | 0.5 |
| 0 | 629 (39%) | 368 (39%) | 261 (40%) |  |
| 1 | 972 (61%) | 586 (61%) | 386 (60%) |  |
| Unknown | 899 | 548 | 351 |  |
| EGFR status |  |  |  | <0.001 |
| 0 | 1,175 (79%) | 823 (82%) | 352 (74%) |  |
| 1 | 310 (21%) | 184 (18%) | 126 (26%) |  |
| Unknown | 1,015 | 495 | 520 |  |
| PD-L1 expression (%) | 46 (39, 53) | 42 (35, 49) | 51 (45, 58) | <0.001 |
| Unknown | 517 | 376 | 141 |  |
| 1Median (IQR); n (%) | | | | |
| 2Wilcoxon rank sum test; Pearson's Chi-squared test | | | | |

Table 3: Overview of covariates of de novo simulated cohort used to showcase the smdi package.

Table : Overview of covariates in simulated example dataset.

| Variable Label | Description | Associated with exposure/outcome | Simulated Missingness [%] |
| --- | --- | --- | --- |
| Age (years) | Age at baseline (continuous) | Yes/Yes | NA |
| Female | Female gender (binary) | Yes/Yes | NA |
| ECOG score | ECOG performance score 0/1 or >1 (binary) | Yes/Yes | MCAR [35%] |
| Smoking history | Smoker vs. non-smoker at baseline (binary) | Yes/Yes | NA |
| Physically active | Physically active vs not active (binary) | Yes/Yes | NA |
| EGFR status | EGFR alteration (binary) | Yes/Yes | MAR [40%] |
| ALK status | ALK translocation (binary) | No/Yes | NA |
| PD-L1 expression (%) | PD-L1 expression in % (continuous) | Yes/Yes | MNAR(value) [20%] |
| Tumor histology | Tumor histology squamous vs nonsquamous (binary) | No/Yes | NA |
| Socio-economic status | Socio-economic status (multi-categorical) | No/No | NA |
| History of COPD | History of COPD (binary) | No/No | Auxiliary to smoking |
| Follow-up (years) | Censoring time (years) | NA | NA |
| Deceased | Indicator if patient experienced outcome | NA | NA |

# Figures

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| Figure 1: Overview of all smdi functions and suggested workflow to conduct missing data diagnostics. \*gg\_miss\_upset() and md.pattern() are re-exports of the naniar and mice package, respectively. |