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

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**Analytical code and data sharing statement:** This manuscript was written using Quarto version 1.3.433 (<https://quarto.org/>) and R version 4.1.2. All R code, materials and depedencies can be found at <https://gitlab-scm.partners.org/drugepi/smdi-manuscript>. The R package presented in this study can be downloaded from CRAN via install.packages("smdi") or from [https://janickweberpals.gitlab-pages.partners.org/smdi](https://janickweberpals.gitlab-pages.partners.org/smdi/).

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# Abstract

145 words/150 words

**Objectives**

Partially observed confounder data are a major challenge for the statistical analysis of electronic health records (EHR). While analytic approaches exist (e.g., multiple imputation), assumptions on underlying missingness patterns and mechanisms must hold. We aimed to develop a toolkit to streamline missing data diagnostics to scrutinize if certain analytic approaches are viable options.

**Materials and Methods**

We developed the smdi (structural missing data investigations) R package based on results of a previous simulation study which considered structural assumptions of common missing data mechanisms in EHR.

**Results**

smdi enables users to run principled missing data investigations on partially observed confounders and implement functions to visualize, describe, and infer potential missingness patterns and mechanisms based on observed data.

**Conclusions**

The smdi R package is freely available on CRAN and GitLab (<https://gitlab-scm.partners.org/janickweberpals/smdi>) and can give valuable insights into underlying missingness patterns and mechanisms and thereby help improve the robustness of real-world evidence studies.

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| Lay Summary |
| As opposed to clinical trials, which are designed to collect data for research purposes in a harmonized manner, real-world data are typically generated for administrative purposes (e.g., health insurance claims for billing purposes) or clinical documentation (e.g., electronic health records). Hence, confounders and prognostic factors, which need to be balanced between treatment groups to infer causal treatment effects, are usually not available for all patients at all necessary time points which leads to missing data. If the underlying missingness mechanisms of such factors is not at random, e.g., patients with higher levels of a prognostic biomarker are more likely to have missing data, this can lead to bias in the resulting effect estimates for the studied treatments if common missing data analysis methods like complete case analysis or imputation are used. Hence, it is of utmost importance to investigate the potential patterns and mechanisms to know if assumptions for common analytic methods hold. Here, we present the smdi R package, which enables researchers to perform such principled missing data investigations on partially observed confounders. The smdi package implements functions to visualize and describe missing data and to infer potential missingness patterns and mechanisms based on observed data. |

# Background and Significance

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

In order to make informed decisions about the most appropriate analytic approach, it is crucial to investigate the potential patterns and mechanisms that underlie the partially observed confounder (POC) data (see definitions box) [7–9]. Usually these are not known for a given RWE study, but guidance frameworks have suggested various routine diagnostics to investigate missing data patterns and mechanisms. These methods comprise standard procedures such as comparing baseline characteristics and outcomes between patients with and without the POC [10–14], checking the ability to predict missingness [11] and assessing if causal relationships between variables and their missingness are recoverable based on available data [15] using 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 such diagnostics is time-consuming, tedious and consequently not often performed [19–21].

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| Definitions: Basic missing data taxonomies. |
| Patterns (adapted 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 [11]  * **Missing completely at random (MCAR)**: The missingness does not depend on any other observed or unobserved covariate(s). * **Missing at random (MAR)**: The missingness depends and can be explained by other observed covariates. * **Missing not at random (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). |

Given these limitations, we have recently developed and evaluated a principled approach combining multiple missing data diagnostics using an US EHR-claims database linkage [22]. The results of this large-scale study revealed that the combination of these diagnostics characterized missing data mechanisms well and provided helpful guidance for the appropriate choice of analytic methods to handle POC data.

# Objective

To streamline implementation of routine missing data diagnostics for POC data in RWE studies, we developed the smdi (structural missing data investigations) R package [23].

# Materials and Methods

The smdi R package was written in R language (version 4.2.1). The package is available on CRAN (<https://cran.r-project.org/web/packages/smdi>) and GitLab (<https://gitlab-scm.partners.org/janickweberpals/smdi>) and can be installed via install.packages("smdi"). To ensure quality, we implemented comprehensive unit tests with a coverage of 95.81% and established automated R CMD checks [24] via continuous integration and deployment. Additional resources such as documentation and vignettes are provided on the package website: <https://janickweberpals.gitlab-pages.partners.org/smdi>.

# Results

## Main Package Functions

[Figure 1](#fig-workflow) illustrates the recommended workflow to systematically approach diagnostics on POCs.

The workflow is generally categorized into descriptives, pattern diagnostics, and inferential diagnostics on potentially underlying missingness mechanisms. In this section, we cover the principles behind the main package functions, a selection of parameters users can specify, the returned results and how these can be interpreted. Examples are illustrated using a synthetic dataset that is part of the package and simulates an oncology cohort with a binary exposure, a time-to-event outcome and several baseline confounders and prognostic covariates including three POCs (EGFR and PD-L1 [biomarkers] and ECOG [performance score]) following MCAR, MAR and MNAR mechanisms (more details: <https://janickweberpals.gitlab-pages.partners.org/smdi/articles/a_data_generation.html>).

For all functions in the smdi package, a *dataframe* is expected (data parameter) as input with a format where one row represents one unique patient and the columns represent relevant variables, i.e., exposure, outcome, fully observed covariates and the POCs. 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, users have the option to specify a vector with the column name(s) of the POC(s) that should be investigated (covar parameter). If nothing is specified, all functions automatically consider any variable in the dataframe that exhibits at least one missing value.

### Descriptives and Pattern Diagnostics

As a first step to explore the missingness in new datasets, the smdi package provides a few basic functions to describe and summarize missingness across all covariates. The smdi\_summarize() function returns the amount and proportion of missing observations, which can also be stratified by a grouping variable. The smdi\_vis() function returns a corresponding bar chart plot (example [Figure 2](#fig-examples) a).

To visually inspect potential missing data patterns, we re-exported the gg\_miss\_upset() function of the naniar package [25]. This function uses a set visualization technique to visually infer potential (non-)monotone patterns based on the number of intersecting missing observations across all POCs [26]. For example, a monotone pattern would be visually evident if, for a set of two or more variables (e.g., lab1, lab2), all or the majority of missing records would be observed for both variables simultaneously (example [Figure 2](#fig-examples) b).

### Inferential Three Group Diagnostics

The core functions to infer potentially underlying missingness mechanisms are categorized into three group diagnostics based on their general analytic properties (**Table 1**).

#### 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 POC. According to Rubin’s framework [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 POC. 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 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 ASMD along with a corresponding range of minimum and maximum AMSDs for each POC, respectively. The object also returns detailed ‘Table 1’s’ and plots [30] for each POC displaying the distributions of observed covariates and resulting ASMDs between patients with and without an observed value for the POC (example [Figure 2](#fig-examples) c).

The smdi\_hotelling() and smdi\_little() functions complement the smdi\_asmd() function by examining differences in patient characteristics as a formal statistical hypothesis test. Hotelling’s test [12,31] formalizes this as a multivariate t-test, which means that smdi\_hotelling() returns a test statistic and p-value for each POC. In contrast, smdi\_little() [13,25] computes a single global chi-square test statistic and p-value across all POCs with the null hypothesis that the data is (globally) MCAR.

#### Group 2 Diagnostics

Group 2 diagnostics assess the ability to predict missingness based on observed covariates via the smdi\_rf() function. This function trains and fits a random forest classification model [11,32] to predict the missing indicator of each POC 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 indicate the model is unable to discriminate missing vs. observed values based on available data; this could be due to a mechanism that is close to MCAR or one where the missingness is associated with unmeasured data (MNAR).

The function returns an object of class *rf* which generically prints an overview of the AUC value of each POC. The AUC is based on the prediction made in the respective test dataset which is sampled as part of the function and for which the train-test split ratio can be specified (train\_test\_ratio parameter). The *rf* object further returns a graph for each POC displaying the relative importance of the predictors in the training dataset expressed as the mean decrease in accuracy (example [Figure 2](#fig-examples) d). 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 model. In case of inflated AUC values (>0.9), the function prompts a message to the user reporting the most important predictor. If in such a scenario another POC is identified as a perfect predictor, the presence of a monotone missing data pattern may be likely in which case it is recommended to run the diagnostics for each POC independently rather than jointly.

#### Group 3 Diagnostics

The third group of diagnostics with the smdi\_outcome() function examines the association of the missingness indicator of the POC and the outcome under study. The function computes both a univariate model and a model adjusted for all other covariates in the dataset. In preceding simulations, we discerned distinct patterns in both univariate and adjusted associations between the missing indicator and the outcome, closely mirroring simulated missingness mechanisms [22]. As expected, under a MCAR mechanism there was no difference in the outcome between patients with and without a value for the POC. Under MAR, given that missingness can be explained by observed covariates, a spurious association in the univariate model disappeared after adjustment. If the missingness followed any MNAR mechanism, an association was observed regardless of adjustment.

Currently, smdi\_outcome() supports three outcome regression types: linear regression (*lm* [33]) for continuous outcomes, logistic regression (*glm* [33]) for binary outcomes and a Cox proportional hazards model (*coxph* [34]) for time-to-event outcomes. Besides the the regression type (model parameter), users need to specify the column containing the outcome using the form\_lhs parameter (e.g., Surv(eventtime, status) in case of a Cox model). The function returns a table with univariate and adjusted beta coefficients and 95% confidence intervals for each POC.

#### smdi\_diagnose() to compute all three group diagnostics

Finally, the smdi\_diagnose() function enables users to compute all three group diagnostics with a single function call.

# minimal example of a smdi\_diagnose() function call  
smdi\_diagnose(  
 data = smdi\_data,  
 model = "cox",  
 form\_lhs = "Surv(eventtime, status)",  
 n\_cores = 3  
 )

The function returns an object of class *smdi* containing a table with the results of all diagnostics for each specified POC and Little’s test p-value across all covariates (**Table 2**). By cross-checking all resulting diagnostic parameters to expected estimates ([Figure 3](#fig-results), [22]), the diagnostics can provide valuable insights into underlying missingness mechanisms and thereby help elucidate if analytic approaches such as imputation analyses are viable options.

# Discussion

Missing data are ubiquitous in EHR and may lead to bias if not handled appropriately. We developed smdi to streamline routine diagnostics of missing data.

The package also has limitations, such that the true underlying missingness generating mechanism can never be inferred with absolute certainty from the observed data. Hence, it’s important to complement diagnostic results with substantive expert knowledge to factor in how covariates are measured in routine care and contextualize potential reasons for missingness.

## Conclusions

The smdi package is a powerful and convenient tool to implement principled routine missing data diagnostics in RWE studies. This will improve the robustness of studies involving POCs by elucidating if certain analytic approaches are viable for a given dataset.

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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: Example output of the smdi\_diagnose() function applied to the examplary smdi\_data dataset.

| Covariate | ASMD (min/max)*1* | p Hotelling*1* | AUC*2* | beta univariate (95% CI)*3* | beta (95% CI)*3* |
| --- | --- | --- | --- | --- | --- |
| ecog\_cat | 0.029 (0.003, 0.071) | 0.783 | 0.510 | -0.06 (95% CI -0.16, 0.03) | -0.06 (95% CI -0.16, 0.03) |
| egfr\_cat | 0.243 (0.010, 0.485) | <.001 | 0.629 | 0.06 (95% CI -0.03, 0.15) | -0.01 (95% CI -0.10, 0.09) |
| pdl1\_num | 0.062 (0.019, 0.338) | <.001 | 0.516 | 0.12 (95% CI 0.01, 0.23) | 0.11 (95% CI -0.00, 0.22) |
| p little: <.001, Abbreviations: ASMD = Median absolute standardized mean difference across all covariates, AUC = Area under the curve, beta = beta coefficient, CI = Confidence interval, max = Maximum, min = Minimum | | | | | |
| *1*Group 1 diagnostic: Differences in patient characteristics between patients with and without covariate | | | | | |
| *2*Group 2 diagnostic: Ability to predict missingness | | | | | |
| *3*Group 3 diagnostic: Assessment if missingness is associated with the outcome (univariate, adjusted) | | | | | |

# 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. |

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| Figure 2: Exemplary visual outputs of the a) smdi\_vis(), b) gg\_miss\_upset(), c) smdi\_asmd() and d) smdi\_rf() functions, respectively. |

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| Figure 3: Example of how smdi diagnostics can be applied to compute and compare diagnostic parameters of partially observed covariates to expected parameters of common missingness mechanisms based on a former large-scale simulation study [22]. |