

smdi

An R package to perform routine structural missing data investigations in real-world data

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Disclosures



Disclosures

- Janick Weerpals reports prior employment by Hoffmann-La Roche and previously held shares in Hoffmann-La Roche
- This project was supported by Task Order 75F40119F19002 under Master Agreement 75F40119D10037 from the U.S. Food and Drug Administration (FDA)

Background

Administrative insurance claims databases are increasingly linked to **electronic health records (EHR)** to improve confounding adjustment for variables which cannot be measured in administrative claims

Examples:

- Labs (HbA1c, LDL, etc.)
- Vitals (Blood pressure, BMI, etc.)
- Disease-specific data (cancer stage, biomarkers, etc.)
- Physician assessments (ECOG, etc.)
- Lifestyle factors (smoking, alcohol, etc.)

These covariates are often just partially observed for various reasons:

- Physician did not perform/order a certain test
- Certain measurements are just collected for particularly sick patients
- Information is ‘hiding’ in unstructured records, e.g. clinical notes

Knowledge gaps and objectives

Missing data in confounding factors are frequent



Two common missing data taxonomies

- **Mechanisms:** Missing completely at random (MCAR), at random (MAR) and not at random (MNAR)
- **Patterns:** Monotone, Non-monotone

Unresolved challenges for **causal inference**:

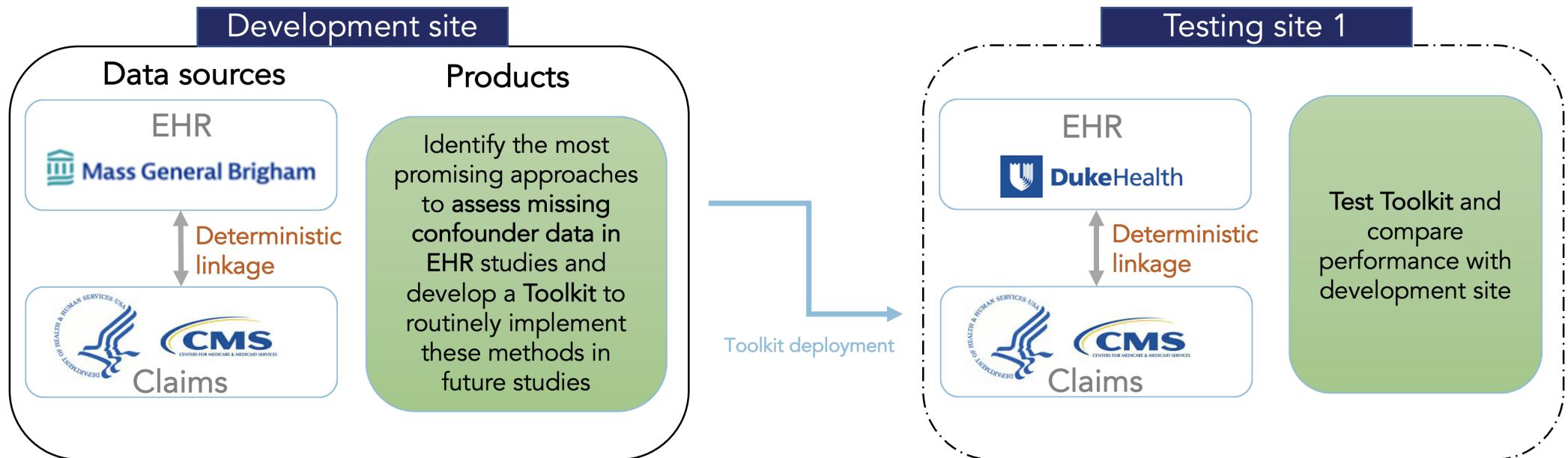
- In an empirical study, it is usually unclear which of the missing data mechanisms and patterns are dominating.
- How do any of these mechanisms relate to bias in a given RWD study, given the strength of correlations between exposure, covariates and outcomes in **high-dimensional covariate spaces (e.g., database linkages)?**

Objectives

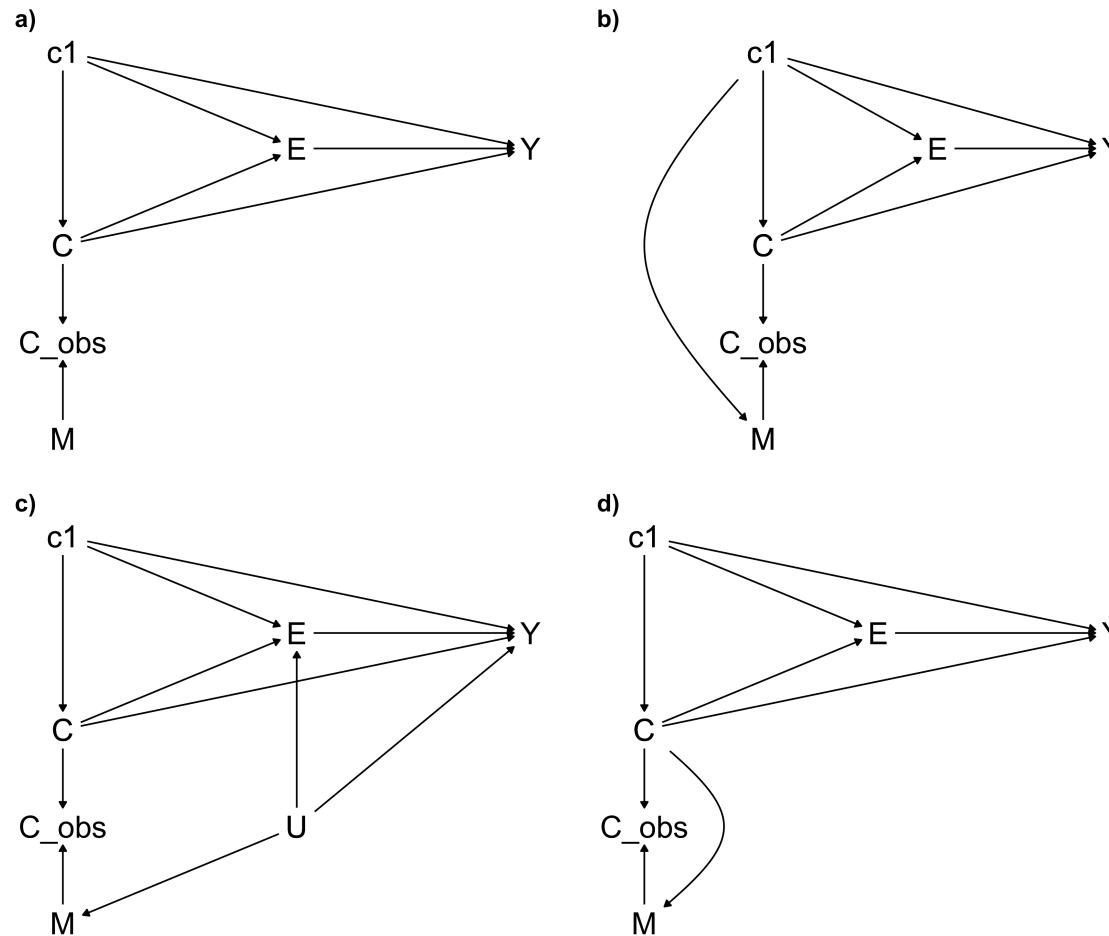


Objectives of the Sentinel Innovation Center Causal Inference Workstream

- Develop a framework and tools to assess the structure of missing data processes in EHR studies
- Connect this with the most appropriate analytical approach, followed by sensitivity analyses
- Develop an **R package** to implement framework and missing data investigations on a routine basis



Assumed missingness structures



Causal diagrams/M-graphs^{1,2} provide a more natural way to understand the assumptions regarding missing (confounder) data for a given research question, Legend: a) Missing completely at random (MCAR), b) Missing at random (MAR), c) Missing not at random 1 (MNAR unmeasured), d) Missing not at random 2 (MNAR value), Notation: E = Exposure, Y = Outcome, c_1 = Fully observed confounders, C = Confounder of interest, C_{obs} = Observed portion of C, M = Missingness indicator

Missing data diagnostics

	Group 1 Diagnostics	Group 2 Diagnostics	Group 3 Diagnostics
	Absolute standardized mean difference (ASMD)	P-value Hoteling/Little	AUC (are under the receiver operating curve)
Purpose	Comparison of distributions between patients with vs w/o observed value of the partially observed covariate	Assessing the ability to predict missingness based on observed covariates	Check whether missingness of a covariate is associated with the outcome (differential missingness)
Example value	ASMD = 0.1	p-value <0.001	AUC = 0.5 log HR = 0.1 (0.05 to 0.2)
Interpretation	<p><0.1*: missingness is not associated with other observed covariates may be completely at random</p> <p>>0.1*: missingness differs between patients and observed covariates can explain difference</p> <p>* Equivalent to propensity score-based balance measures (Austin PC, Multivariate Behavioral Research, 46:3, 399-424 (2011))</p>	<p>Low p-values: Indicate differences in covariate distributions and null hypothesis would be rejected (\neqMCAR)</p> <p>Hotelling H. Ann Math Stat. 2(3):360-378. (1931) & Little RJA. J Am Stat Assoc. 83(404):1198-1202. doi:10.2307/2290157 (1988)</p>	<p>Values around 0.5: Indicate random prediction (MCAR)</p> <p>Values meaningfully above 0.5 indicate stronger correlations between covariates (which can be determined!) and missingness (~MAR)</p> <p>MCAR: No association in neither crude nor adjusted model MAR: Association in crude but not adjusted model MNAR: If there was a meaningful difference also after comprehensive adjustment (log HR), this may be indicative of differential MNAR scenarios</p>

Plasmode simulation - results

Observations

- Large scale simulation revealed characteristic patterns of the diagnostic parameters matched to missing data structure
- The observed diagnostic pattern of a specific study will give insights into the likelihood of underlying missingness structures

Expected parameter constellations	Group 1 Diagnostics		Group 2 Diagnostics		Group 3 Diagnostics	
	ASMD (Absolute standardized mean difference)	P-value Hoteling/Little	AUC (are under the receiver operating curve)	Log HR (crude)	Log HR (adjusted)	
MCAR	0.05	0.5	0.50	-0.01	0.00	
MAR	0.20	<.001	0.58	0.53	0.00	
MNAR _{unmeasured}	0.09	0.02	0.54	0.43	0.31	
MNAR _{value}	0.06	0.10	0.53	0.04	0.10	

Plasmode simulation results averaged across all scenarios and simulated datasets.

Plasemode simulation - results

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Let's have a look at some EHR examples:

Covariate	ASMD (min to max)	P-value	AUC	Log HR (crude, 95% CI)	Log HR (adjusted, 95% CI)
EGFR (cancer biomarker)	0.24 (0.01 to 0.49)	<.001	0.63	0.06 (-0.03 to 0.15)	-0.01 (-0.10 to 0.09)

The observed diagnostic pattern of a specific study will give insights into the likelihood of underlying missingness structures

Plasemode simulation - results

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EGFR (cancer biomarker)	0.24 (0.01 to 0.49)	<.001	0.63	0.06 (-0.03 to 0.15)	-0.01 (-0.10 to 0.09)
ECOG (performance status)	0.03 (0.00 to 0.07)	0.78	0.51	-0.06 (-0.16 to 0.03)	-0.06 (-0.16 to 0.03)

The observed diagnostic pattern of a specific study will give insights into the likelihood of underlying missingness structures

The `smdi` package aims to streamline these structural missing data diagnostics (and more)!

... let's walk through some examples and functionalities of `smdi`

```
1 library(smdi)
2 library(dplyr)
```

smdi bundled datasets

- The `smdi` package comes with two exemplary **simulated** datasets:
 - `smdi_data` (includes some partially observed covariates)
 - `smdi_data_complete` (complete dataset if you prefer to introduce `NA` yourself)

```

1 smdi_data %>%
2   glimpse()

Rows: 2,500
Columns: 14
$ exposure      <int> 1, 1, 0, 1, 1, 0, 1, 1, 0, 1, 1, 0, 0, 1, 1, 0, 0, ...
$ age_num        <dbl> 35.24, 51.18, 88.17, 50.79, 40.52, 64.57, 73.58, 42.38, ...
$ female_cat    <fct> 1, 0, 0, 0, 0, 0, 1, 1, 1, 0, 0, 1, 0, 0, 1, 1, 1, ...
$ smoking_cat   <fct> 1, 1, 0, 1, 1, 0, 1, 1, 1, 0, 0, 1, 1, 1, 1, 0, 1, ...
$ physical_cat  <fct> 0, 1, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 1, 0, 1, 0, ...
$ alk_cat        <fct> 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, ...
$ histology_cat <fct> 1, 1, 0, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, ...
$ ses_cat        <fct> 2_middle, 3_high, 2_middle, 2_middle, 2_middle...
$ copd_cat       <fct> 1, 0, 1, 1, 1, 0, 1, 1, 1, 0, 1, 1, 1, 0, 1, 0, 1, ...
$ eventtime     <dbl> 5.000000000, 4.754220474, 0.253391563, 5.000000000, 5.00...
$ status         <int> 0, 1, 1, 0, 0, 1, 1, 0, 1, 1, 1, 1, 1, 0, 0, 1, 1, ...
$ ecog_cat       <fct> 1, NA, 0, 1, NA, 0, 1, 0, 1, NA, 1, NA, NA, 1, 1, 0, 1, ...
$ egfr_cat       <fct> NA, 0, 1, NA, 1, NA, NA, 0, NA, 0, 1, NA, 0, NA, NA, 0, ...
$ pdl1_num       <dbl> 45.03, NA, 41.74, 45.51, 31.28, NA, 47.28, 37.28, 46.47, ...

```

Descriptives

- Let's start with some light descriptives
- All `smdi` functions automatically include all variables with at least one missing value (default)
- Investigator-specified variables can be selected via the `covar` parameter

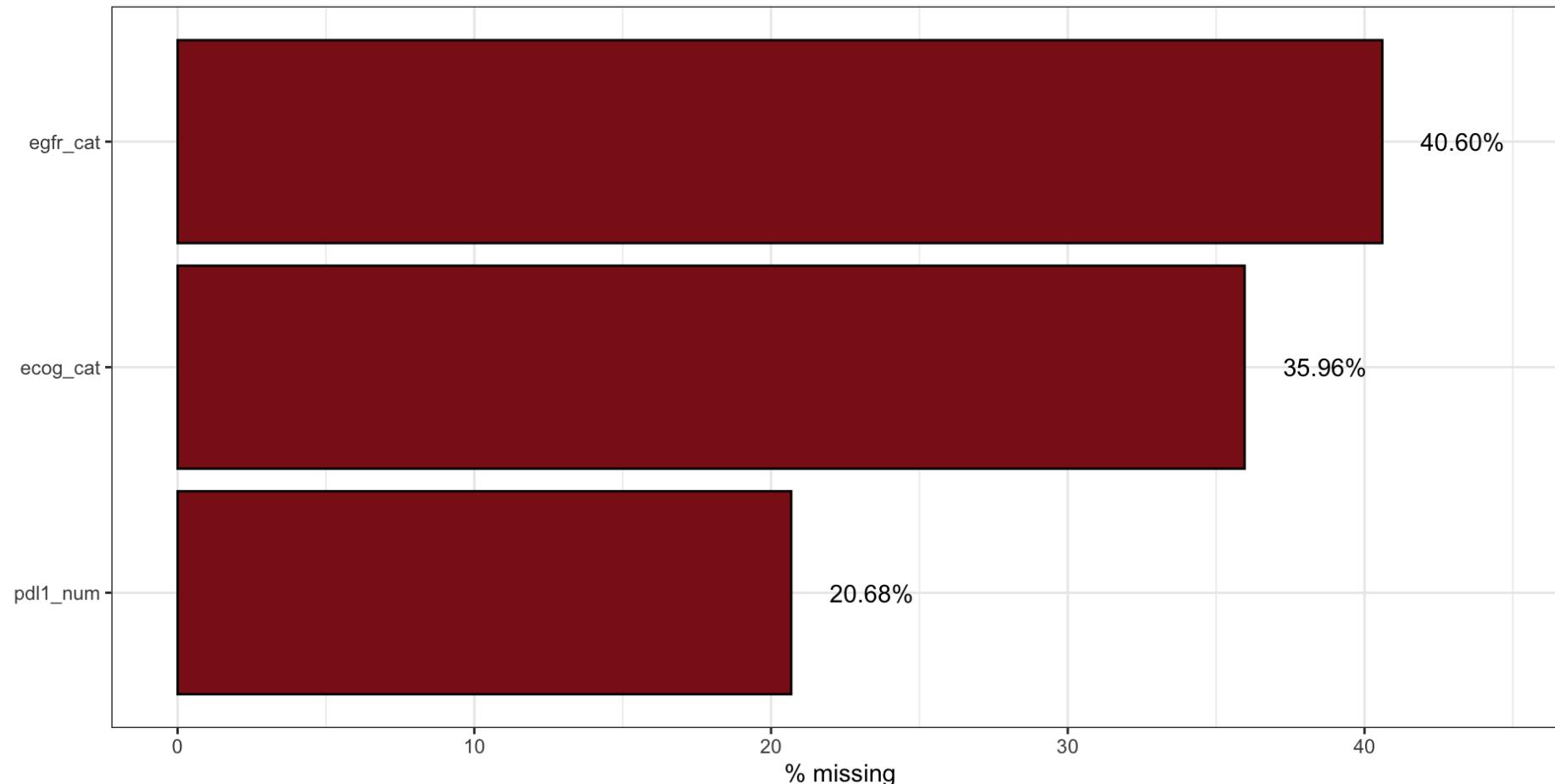
```
1 smdi_data %>%
2   smdi_summarize()

# A tibble: 3 × 4
  covariate n_miss prop_miss prop_miss_label
  <chr>      <int>    <dbl>    <chr>
1 egfr_cat     1015    40.6  40.60%
2 ecog_cat      899    36.0  35.96%
3 pdl1_num      517    20.7  20.68%
```

Descriptives - visual

Overall

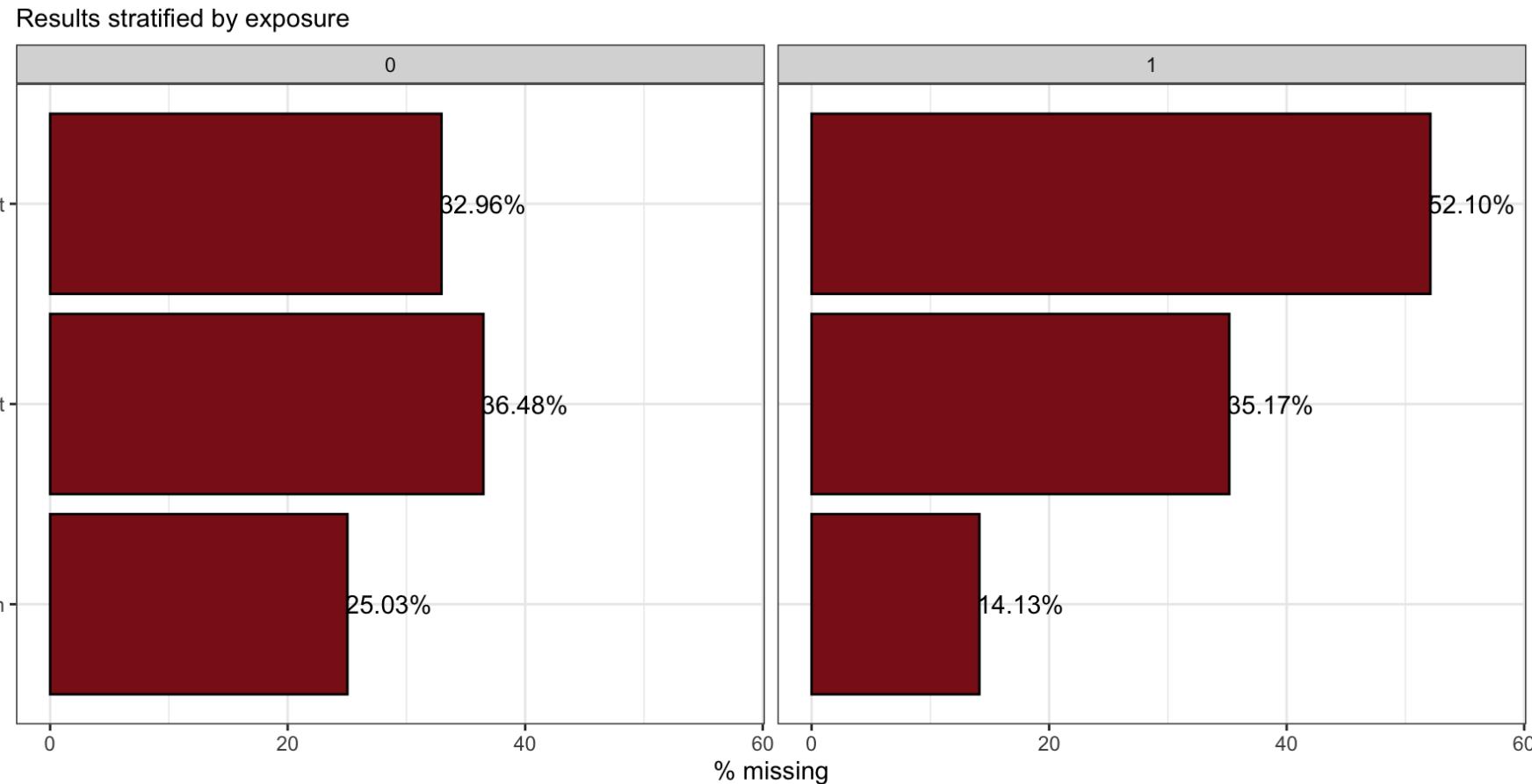
```
1 smdi_data %>%
2   smdi_vis()
```



Descriptives - visual

Stratified by another variable (stratum-specific sample size is the denominator)

```
1 smdi_data %>%
2   smdi_vis(strata = "exposure")
```



Descriptives - pattern

`smdi` uses a *re-export* of the `naniar`³ `gg_miss_upset` and `mice`⁴ `md.pattern` functions to investigate potentially underlying **missing data patterns**

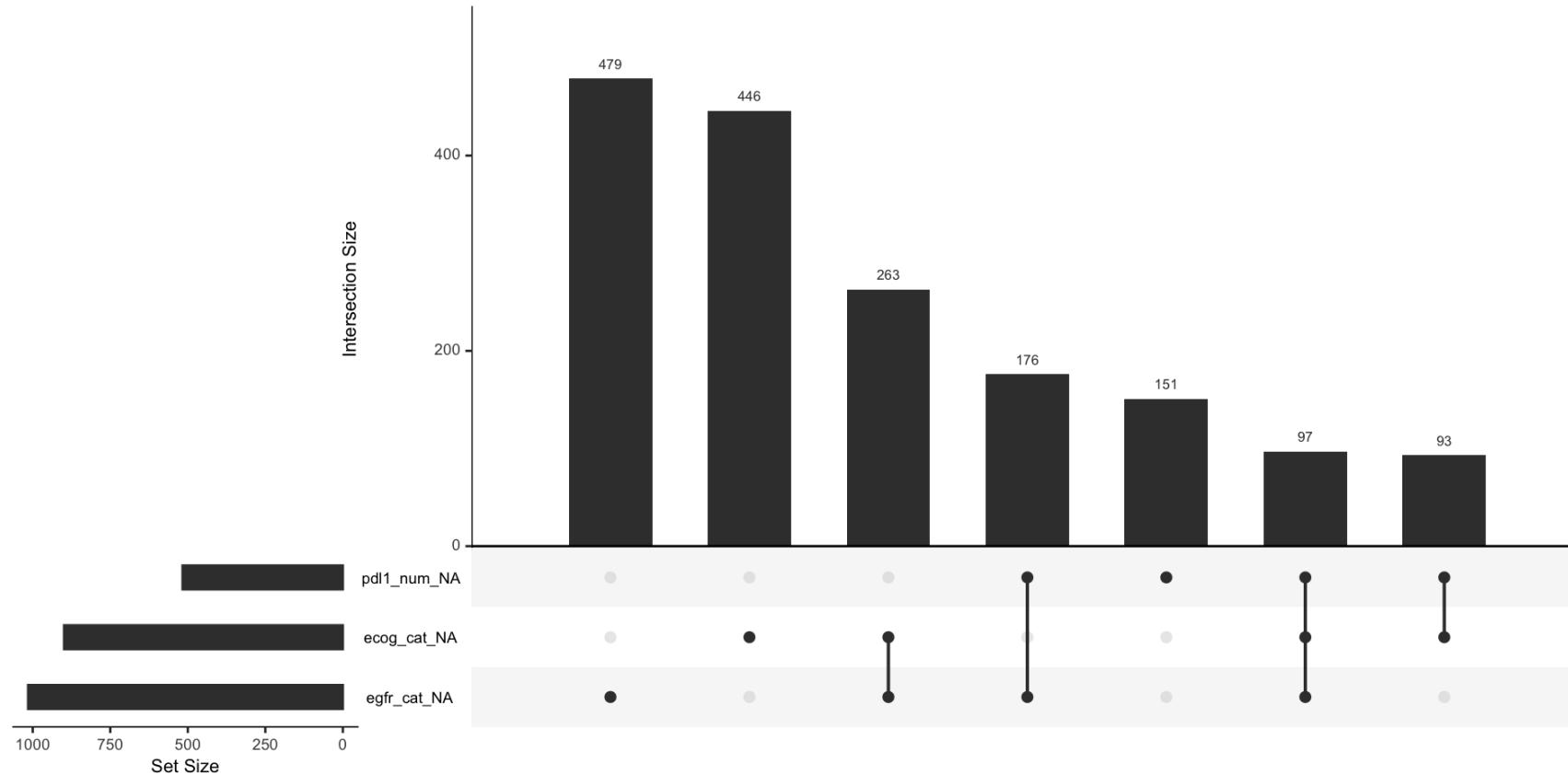
 Note

Monotone and non-monotone (or general). A missing data pattern is said to be *monotone* if the variables Y_j can be ordered such that if Y_j is missing then all variables Y_k with $k > j$ are also missing. This occurs, for example, in longitudinal studies with drop-out. If the pattern is not monotone, it is called *non-monotone* or *general*.⁴

Descriptives - pattern

`smdi` uses a *re-export* of the `naniar3` `gg_miss_upset` function to investigate potentially underlying missing data patterns

```
1 smdi_data %>%
2   gg_miss_upset()
```



smdi_asmd

Group 1 diagnostics: Differences in covariate distributions

```
1 asmd <- smdi_asmd(data = smdi_data, median = TRUE, includeNA = FALSE)
2 asmd
```

```
# A tibble: 3 × 4
  covariate asmd_median asmd_min asmd_max
* <chr>      <chr>       <chr>      <chr>
1 ecog_cat    0.029       0.003     0.071
2 egfr_cat    0.243       0.010     0.485
3 pdl1_num    0.062       0.019     0.338
```

smdi_asmd

Group 1 diagnostics: Differences in covariate distributions

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```

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2 egfr_cat    0.243      0.010      0.485
3 pdl1_num    0.062      0.019      0.338
```

The output returns an *asmd* object that much more information than what is captured in the S3 generic *print* output, e.g. a complete ‘*Table 1*’ that displays the covariate distributions of patients:

```
1 head(asmd$pdl1_num$asmd_table1)
```

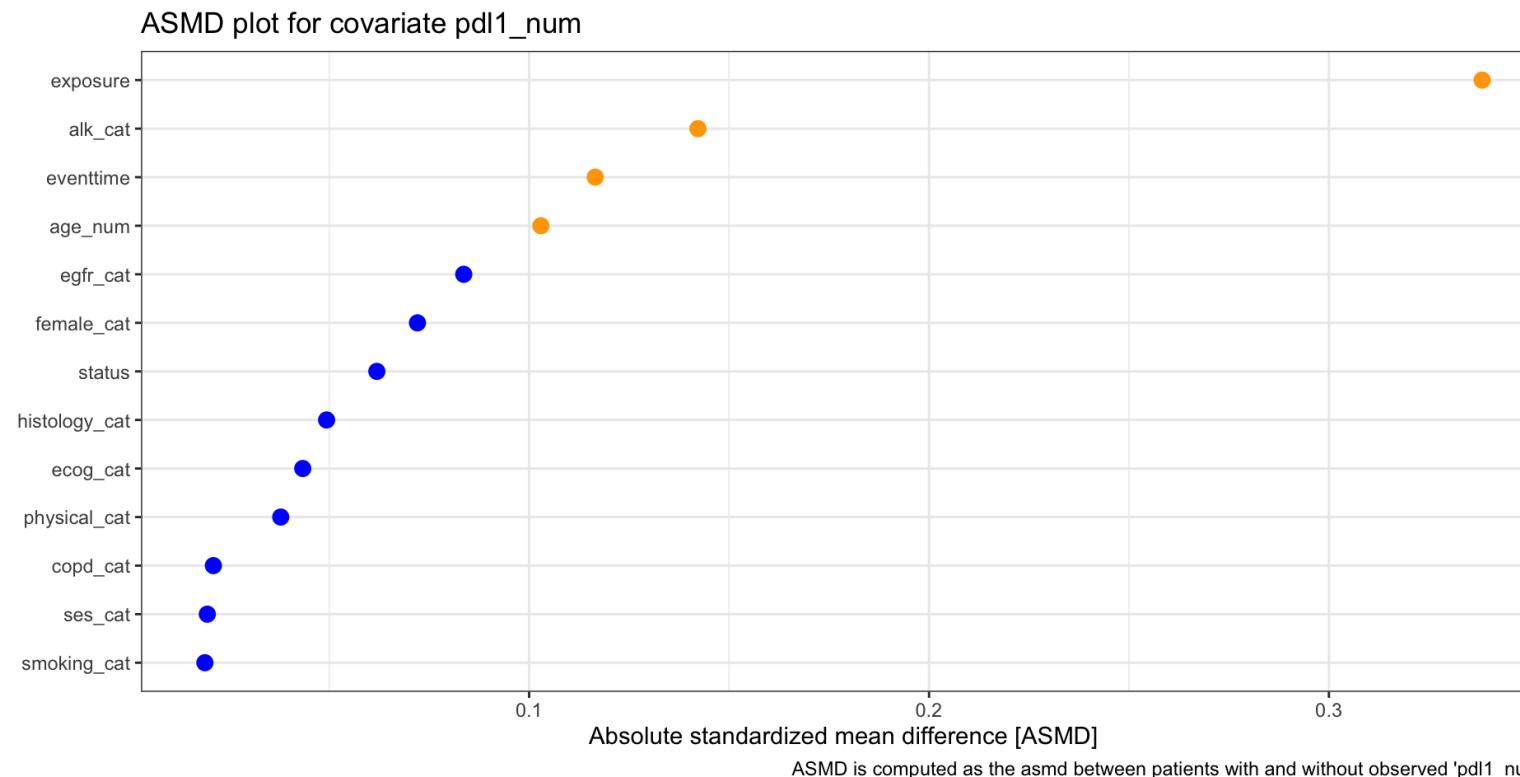
Stratified by pdl1_num_NA						
	0	1	p	test	SMD	
n	" 1983"	" 517"	""	""	""	
exposure (mean (SD))	" 0.43 (0.50)"	" 0.27 (0.45)"	"<0.001"	""	" 0.338"	
age_num (mean (SD))	"60.60 (14.04)"	"62.07 (14.47)"	" 0.036"	""	" 0.103"	
female_cat = 1 (%)	" 717 (36.2)"	" 205 (39.7)"	" 0.157"	""	" 0.072"	
smoking_cat = 1 (%)	" 990 (49.9)"	" 263 (50.9)"	" 0.739"	""	" 0.019"	
physical_cat = 1 (%)	" 707 (35.7)"	" 175 (33.8)"	" 0.476"	""	" 0.038"	

smdi_asmd

Group 1 diagnostics: Differences in covariate distributions

Investigators can also inspect standardized mean differences⁵ by covariate in detail:

```
1 asmd$pdl1_num$asmd_plot
```



smdi_hotelling

Group 1 diagnostics: Differences in covariate distributions

Hotelling's⁶ multivariate t-test examines differences in covariate distributions conditional on having an observed covariate value or not. Rejection of H0 would indicate significant differences between these patient strata.

```
1 smdi_hotelling(data = smdi_data)

covariate hotteling_p
1 ecog_cat      0.783
2 egfr_cat      <.001
3 pdl1_num      <.001
```

smdi_little

Group 1 diagnostics: Differences in covariate distributions

Little's⁷ chi-square test takes into account possible patterns of missingness **across all variables** in the dataset. A high test statistics and low p-value (rejection of H0) would indicate that the **global** missing data generating mechanism is not completely at random.

```
1 smdi_little(data = smdi_data)

$statistic
[1] 801.0009

$df
[1] 86

$p.value
[1] 0

$missing.patterns
[1] 8

attr(,"class")
[1] "little"
attr(,"row.names")
[1] 1
```

smdi_rf

Group 2 diagnostics: Ability to predict missingness

The `smdi_rf` function trains and fits a random forest model to assess the ability to predict missingness for the specified covariate(s).⁸

```
1 auc <- smdi_rf(data = smdi_data, train_test_ratio = c(.7, .3), set_seed = 42, n_cores = 3)
2 auc

# A tibble: 3 × 2
  covariate rf_auc
  * <chr>     <dbl>
1 ecog_cat    0.510
2 egfr_cat    0.629
3 pdl1_num    0.516
```



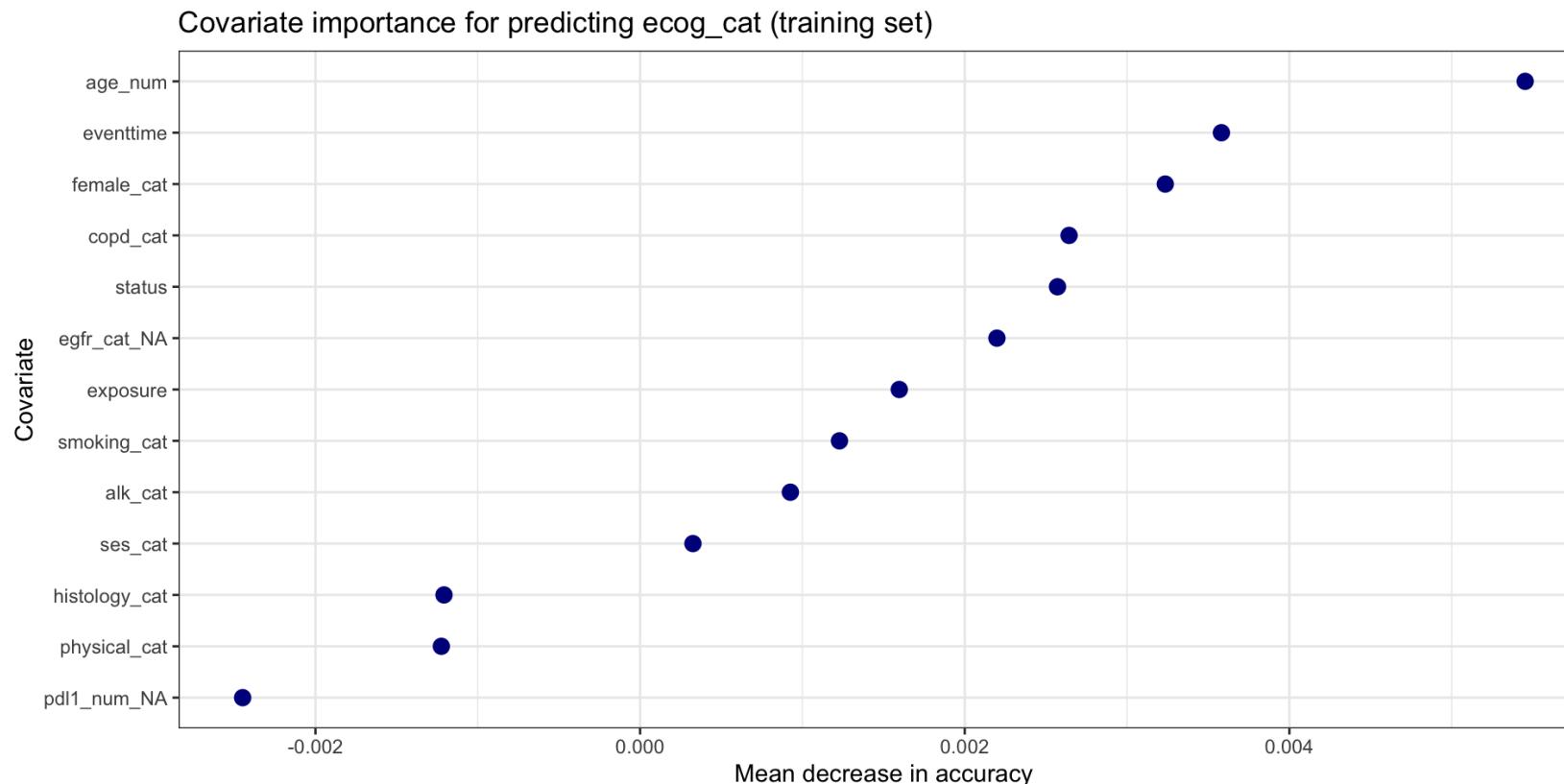
Parallelization

Depending on the amount of data (sample size x covariates), the computation of the function can take some minutes. To speed this up, investigators can parallelize the computation using `n_cores` (UNIX only).

smdi_rf

The resulting `smdi_rf` object provides the flexibility to investigate the covariate importance of predictors which can give important hints on the potentially underlying missing data generating mechanism.

```
1 auc$ecog_cat$rf_plot
```



smdi_outcome

Group 3 diagnostic focuses on assessing the association between the missing indicator of the partially observed covariate and the outcome under study (is the missingness differential?).

```

1 outcome <- smdi_outcome(
2   data = smdi_data,
3   model = "cox",
4   form_lhs = "Surv(eventtime, status)",
5   exponentiated = FALSE
6 )
7
8 outcome

# A tibble: 3 × 3
  covariate estimate_crude      estimate_adjusted
  <chr>     <glue>          <glue>
1 ecog_cat  -0.06 (95% CI -0.16, 0.03) -0.06 (95% CI -0.16, 0.03)
2 egfr_cat   0.06 (95% CI -0.03, 0.15)  -0.01 (95% CI -0.10, 0.09)
3 pdl1_num   0.12 (95% CI 0.01, 0.23)   0.11 (95% CI -0.00, 0.22)

```



Supported regression types

Currently, the main types of outcome regressions are supported, namely *logistic* ([glm](#)), *linear* ([lm](#)) and *Cox proportional hazards* ([survival](#)) models are supported and need to be specified using the `model` and `form_lhs`.

smdi_diagnose



One function to rule them all: `smdi_diagnose`

- Wrapper around all of the aforementioned functions
- Input parameters correspond to parameters of the individual functions

Let's take a look at a most minimal example

```

1 diagnostics <- smdi_diagnose(
2   data = smdi_data,
3   model = "cox",
4   form_lhs = "Surv(eventtime, status)",
5   n_cores = 3
6 )
7
8 diagnostics

smdi summary table:
# A tibble: 3 × 6
  covariate asmd_median_min_max hotteling_p rf_auc estimate_crude
  <chr>      <chr>           <chr>      <chr>    <glue>
1 ecog_cat  0.029 (0.003, 0.071) 0.783      0.510  -0.06 (95% CI -0.16, 0.03)
2 egfr_cat  0.243 (0.010, 0.485) <.001      0.629  0.06 (95% CI -0.03, 0.15)
3 pdl1_num  0.062 (0.019, 0.338) <.001      0.516  0.12 (95% CI 0.01, 0.23)
# i 1 more variable: estimate_adjusted <glue>

p_little: <.001

```

smdi_diagnose

Output is a list that resembles all three group diagnostics validated in the plasmode simulation study...

Covariate-specific table:

```
1 diagnostics$smdi_tbl
# A tibble: 3 × 6
  covariate asmd_median_min_max hotteling_p rf_auc estimate_crude
  <chr>     <chr>           <chr>      <chr>    <glue>
1 ecog_cat  0.029 (0.003, 0.071) 0.783      0.510   -0.06 (95% CI -0.16, 0.03)
2 egfr_cat  0.243 (0.010, 0.485) <.001      0.629   0.06 (95% CI -0.03, 0.15)
3 pdl1_num  0.062 (0.019, 0.338) <.001      0.516   0.12 (95% CI 0.01, 0.23)
# i 1 more variable: estimate_adjusted <glue>
```

Global Little's test p-value:

```
1 diagnostics$p_little
p_little: <.001
```

smdi_style_gt

`smdi_style_gt` takes an object of class `smdi` (i.e., the output of `smdi_diagnose`) and formats it into a **publication-ready** `gt` table:

```
1 diagnostics %>%
2   smdi_style_gt(font_size = 18, tbl_width = 1000)
```

Covariate	ASMD (min/max) ¹	p Hotelling ¹	AUC ²	beta crude (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 (crude, adjusted)

smdi_style_gt

Since `smdi_style_gt` transforms the `smdi` object into an object of class `gt_tbl`, an investigator can also take advantage of all of the `gt` package perks, e.g. exporting the table in different formats, e.g. `.docx`, `.rtf`, `.pdf`, etc.:

```
1 gtsave(  
2   data = smdi_style_gt(diagnostics),  
3   filename = "smdi_table.docx", # name of the final file and file type (e.g., .docx)  
4   path = "." # path where the file should be stored  
5 )
```

Test it out yourself

```
1 # install.packages("devtools")
2 devtools::install_git("https://gitlab-scm.partners.org/janickweberpals/smdi.git")
```

- Vignettes/tutorials: <https://janickweberpals.gitlab-pages.partners.org/smdi>
- Presentation quarto code: <https://github.com/janickweberpals/NESS2023> (accessible after SciComms/FDA approval)
- Presentation slides: <https://janickweberpals.github.io/NESS2023> (accessible after SciComms/FDA approval)

References



References cited in this presentation

1. Choi J, Dekkers OM, Cessie S le. A comparison of different methods to handle missing data in the context of propensity score analysis. *European Journal of Epidemiology*. 2019;34(1):23-36. doi:[10.1007/s10654-018-0447-z](https://doi.org/10.1007/s10654-018-0447-z)
2. Mohan K, Pearl J. Graphical models for processing missing data. *Journal of the American Statistical Association*. 2021;116(534):1023-1037. doi:[10.1080/01621459.2021.1874961](https://doi.org/10.1080/01621459.2021.1874961)
3. Tierney N, Cook D. Expanding tidy data principles to facilitate missing data exploration, visualization and assessment of imputations. 2023;105. doi:[10.18637/jss.v105.i07](https://doi.org/10.18637/jss.v105.i07)
4. Buuren S van, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in r. 2011;45:1-67. doi:[10.18637/jss.v045.i03](https://doi.org/10.18637/jss.v045.i03)
5. Austin PC. Assessing covariate balance when using the generalized propensity score with quantitative or continuous exposures. *Statistical Methods in Medical Research*. 2018;28(5):1365-1377. doi:[10.1177/0962280218756159](https://doi.org/10.1177/0962280218756159)
6. Hotelling H. The Generalization of Student's Ratio. *The Annals of Mathematical Statistics*. 1931;2(3):360-378. doi:[10.1214/aoms/1177732979](https://doi.org/10.1214/aoms/1177732979)
7. Little RJA. A Test of Missing Completely at Random for Multivariate Data with Missing Values. *Journal of the American Statistical Association*. 1988;83(404):1198-1202. doi:[10.1080/01621459.1988.10478722](https://doi.org/10.1080/01621459.1988.10478722)
8. Sondhi A, Weberpals J, Yerram P, et al. A systematic approach towards missing lab data in electronic health records: A case study in non-small cell lung cancer and multiple myeloma. (accepted). *CPT Pharmacometrics Syst Pharmacol*.

smdi - An R package to perform routine structural missing data investigations in real-world data

