smdi

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

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Disclosures

⚠ **Disclosures**

- Janick Weberpals 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

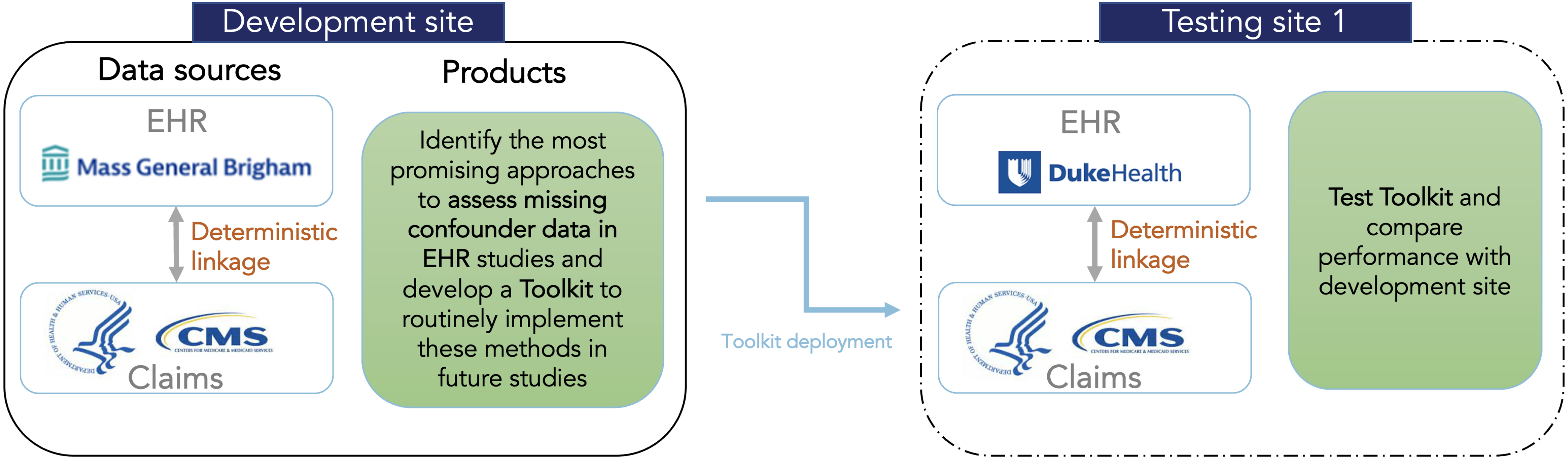
Unresolved challenges for `causal inference`:

- 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 real-world data (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**



Development site

Data sources

Products

EHR

Mass General Brigham

Deterministic linkage

Claims

Identify the most promising approaches to assess missing confounder data in EHR studies and develop a Toolkit to routinely implement these methods in future studies

Toolkit deployment

Testing site 1

EHR

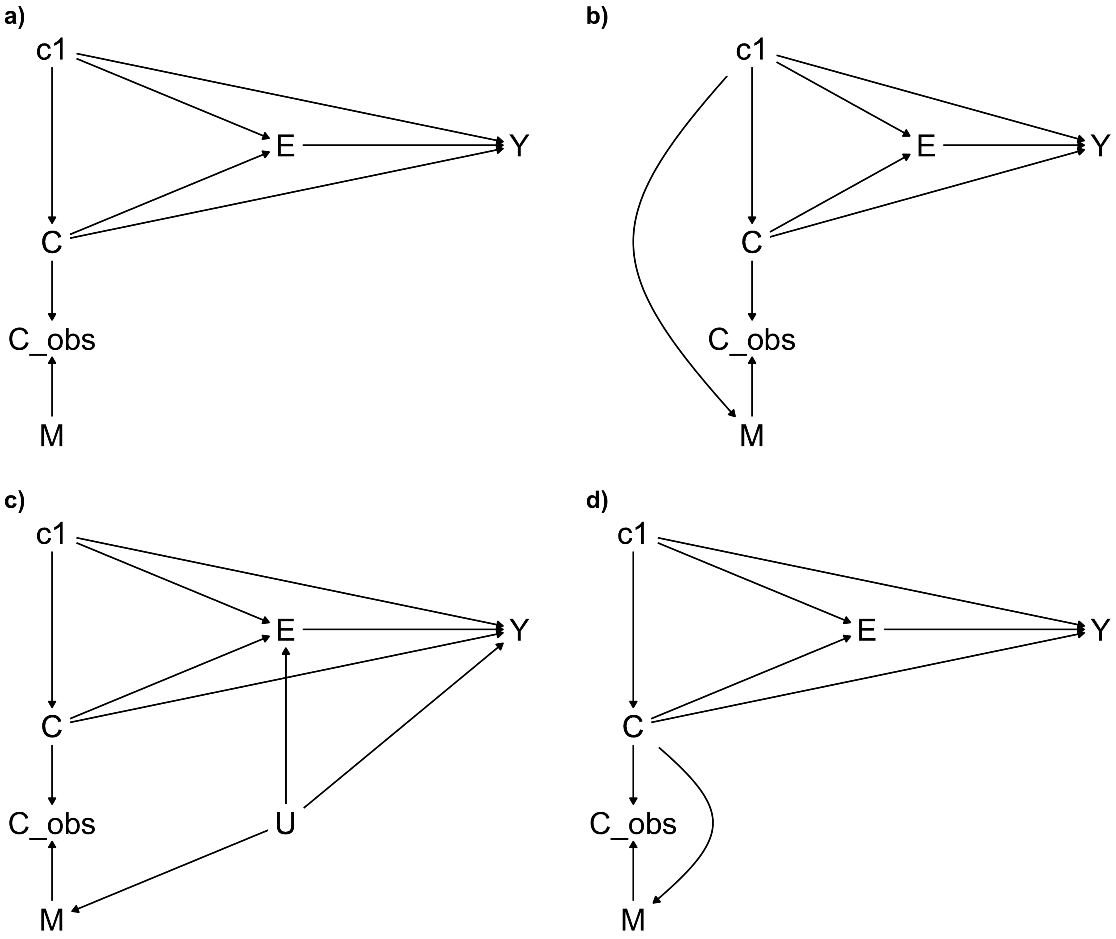
DukeHealth

Deterministic linkage

Claims

Test Toolkit and compare performance with development site

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, C1 = Fully observed confounders, C = Confounder of interest, C_obs = Observed portion of C, M = Missingness indicator

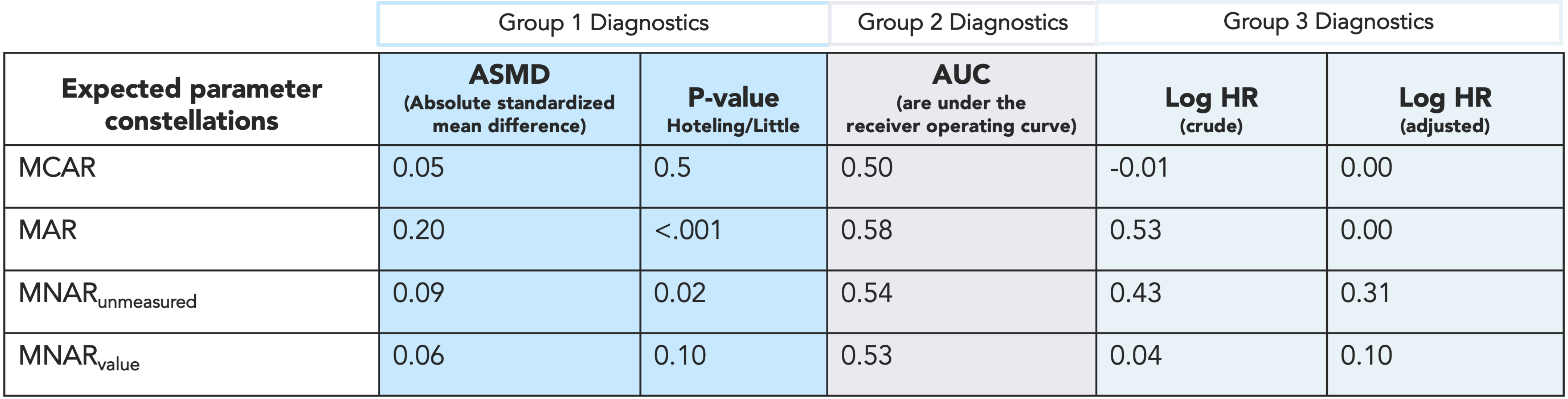
Missing data diagnostics

	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)**	**Log HR (missingness indicator)**
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	<0.1*: missingness is not associated with other observed covariates may be completely at random >0.1*: missingness differs between patients and observed covariates can explain difference * Equivalent to propensity score-based balance measures (Austin PC, Multivariate Behavioral Research, 46:3, 399-424 (2011))	Low p-values: Indicate differences in covariate distributions and null hypothesis would be rejected (≠MCAR) 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)	Values around 0.5: Indicate random prediction (MCAR) Values meaningfully above 0.5 indicate stronger correlations between covariates (which can be determined!) and missingness (~MAR)	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**

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



	Group 1 Diagnostics		Group 2 Diagnostics	Group 3 Diagnostics	
Expected parameter constellations	**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
$\text{MNAR}_{\text{unmeasured}}$	0.09	0.02	0.54	0.43	0.31
$\text{MNAR}_{\text{value}}$	0.06	0.10	0.53	0.04	0.10

Plasmode simulation results averaged across all scenarios and simulated datasets.

Plasmode 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

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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`

```r
library(smdi)
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)

```r
smdi_data %>%
  glimpse()
```

```
Rows: 2,500
Columns: 14
$ exposure      <int> 1, 1, 0, 1, 1, 0, 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, 0, 1, 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, 0, 1,…
$ physical_cat  <fct> 0, 1, 0, 0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 0, 1, 0, 1, 0, 0,…
$ alk_cat       <fct> 0, 0, 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, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0,…
$ ses_cat       <fct> 2_middle, 3_high, 2_middle, 2_middle, 2_middle, 2_middle…
$ copd_cat      <fct> 1, 0, 1, 1, 1, 0, 1, 1, 1, 1, 0, 1, 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, 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

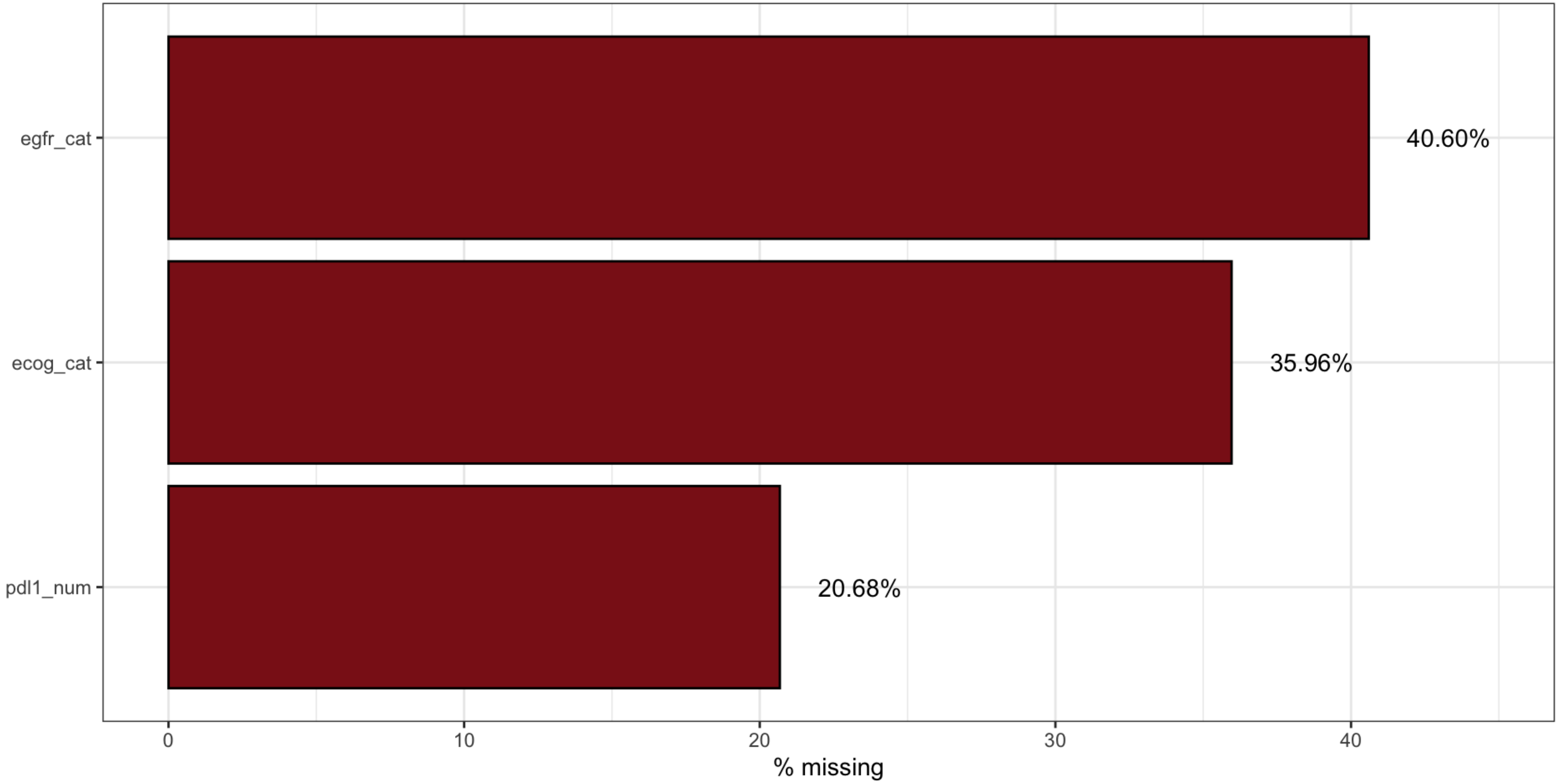
```
smdi_data %>%
  smdi_summarize()
```

```
# 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

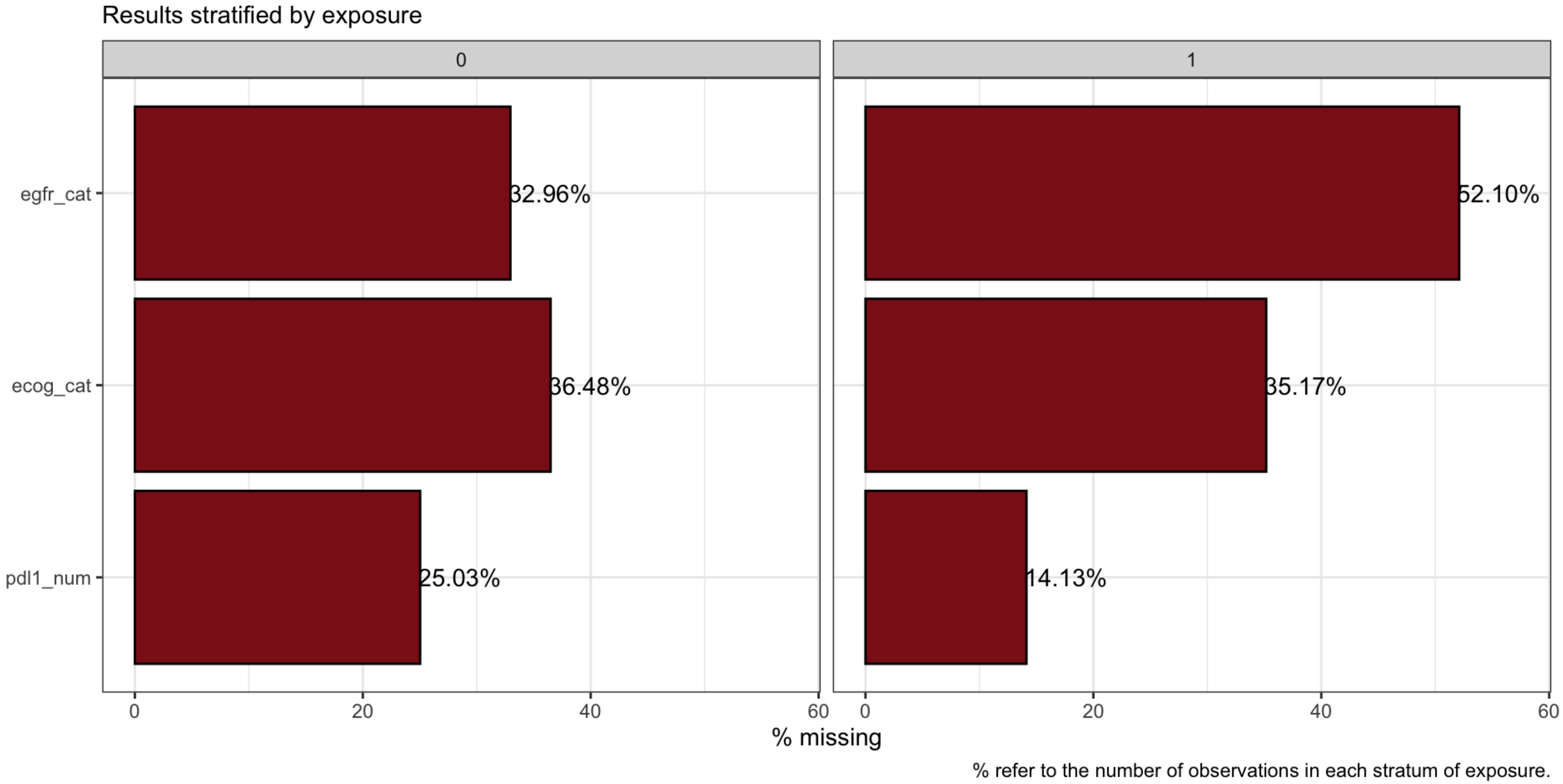
```r
smdi_data %>%
  smdi_vis()
```



Descriptives - visual

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

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



Descriptives - pattern

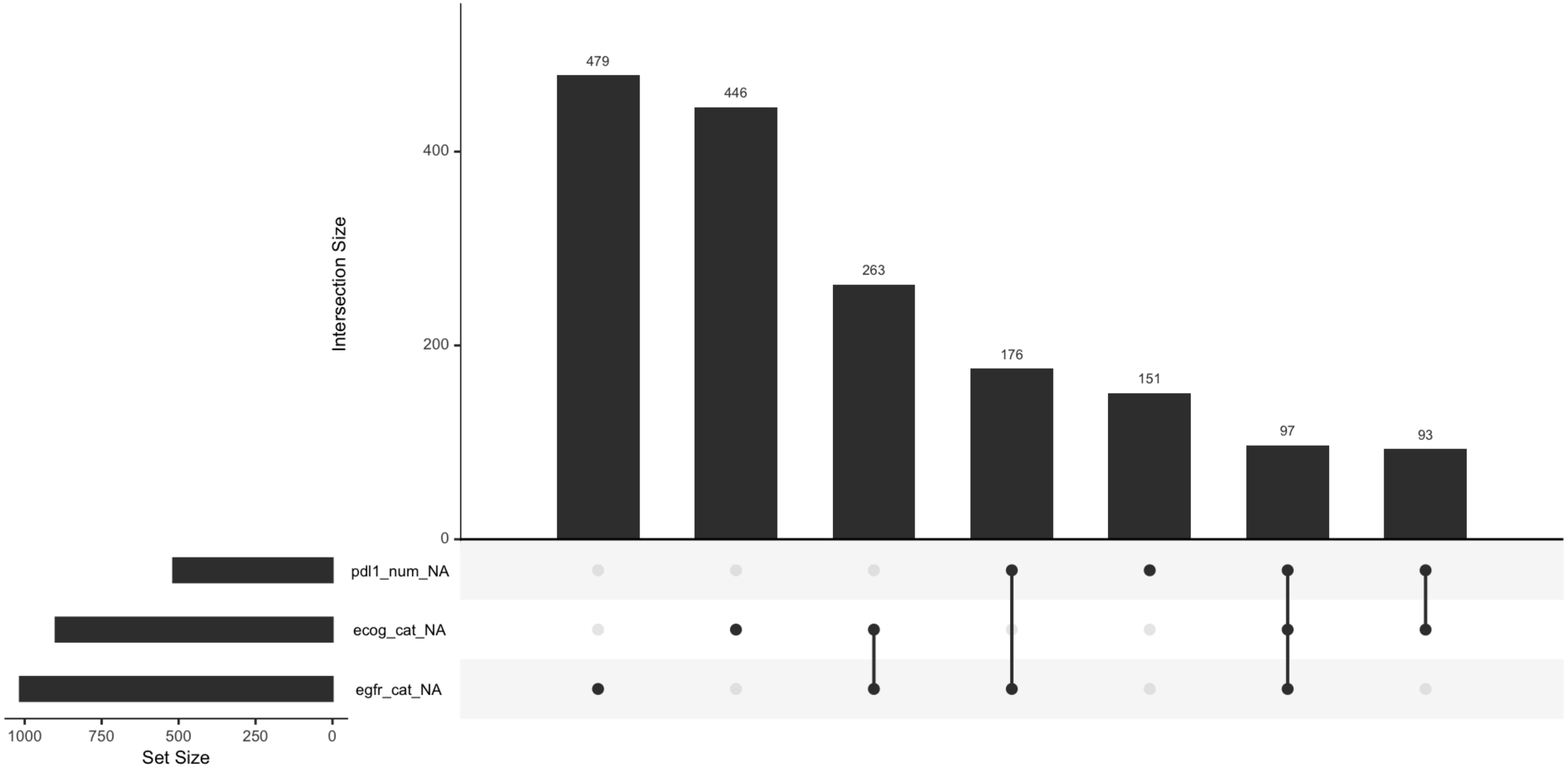
`smdi` uses a *re-export* of the **naniar**[3] `gg_miss_upset` and **mice**[4] `md.pattern` functions to investigate potentially underlying **missing data patterns**

> ⓘ **Note**
>
> *Monotone and non-monotone (or general)*. A missing data pattern is said to be *monotone* if the variables can be ordered such that if is missing then all variables with 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 **naniar**[3] `gg_miss_upset` function to investigate potentially underlying **missing data patterns**

```r
smdi_data %>%
  gg_miss_upset()
```



smdi_asmd

> Group 1 diagnostics: Differences in covariate distributions

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

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asmd
```

```
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  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
```

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:

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

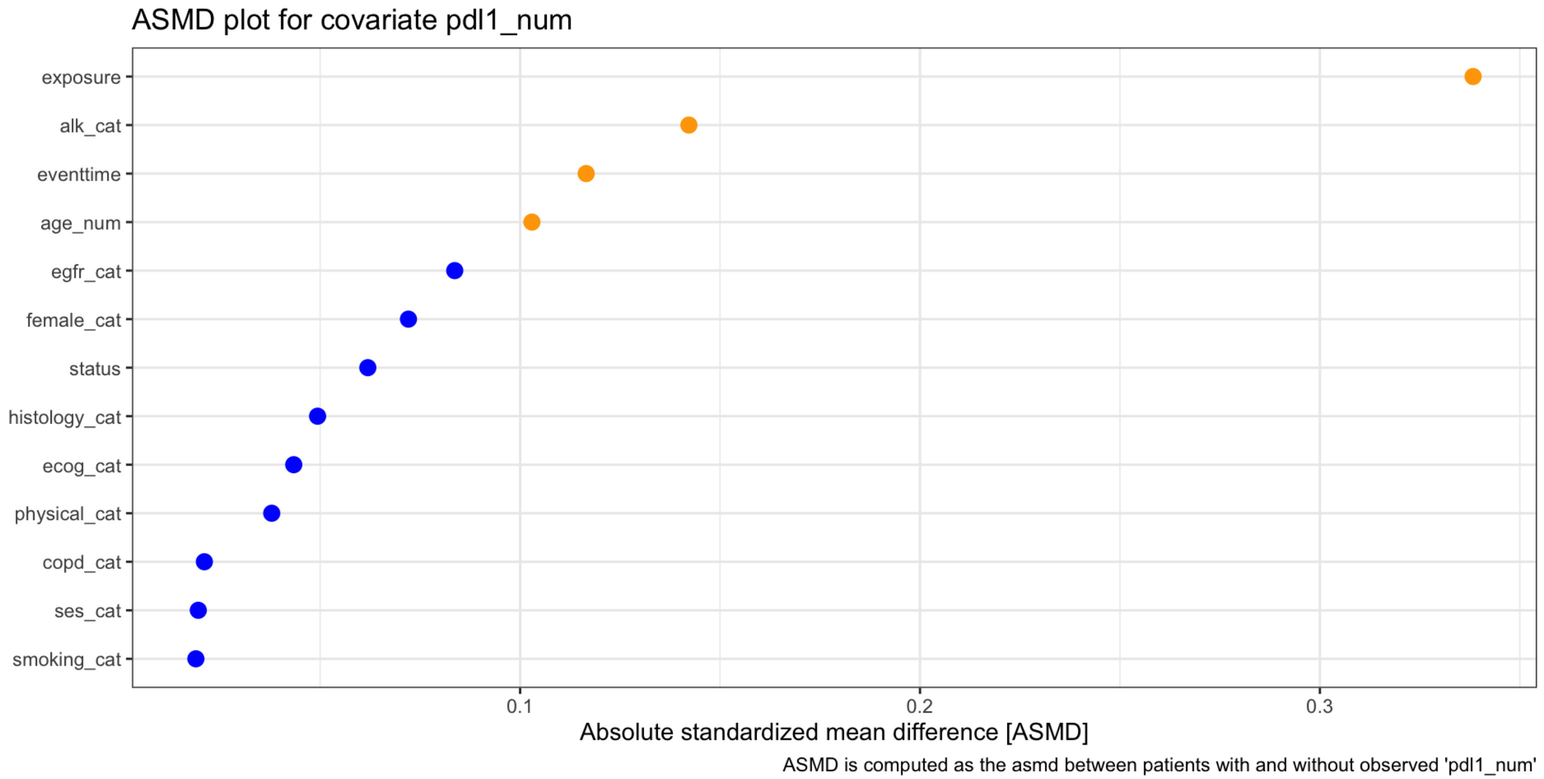
```
                      Stratified by pdl1_num_NA
                       0                1                p        test SMD
  n                    " 1983"          "  517"          ""       ""   ""
  exposure (mean (SD)) " 0.43 (0.50)"  " 0.27 (0.45)"  "<0.001" ""   " 0.338"
  age_num (mean (SD))  "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 differences[5] by covariate in detail:

```
asmd$pdl1_num$asmd_plot
```



smdi_hotelling

> Group 1 diagnostics: Differences in covariate distributions

Hotelling’s[6] multivariate t-test examines differences in covariate distributions conditional on having an observed covariate value or not. Rejection of would indicate significant differences between these patient strata.

```r
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's[7] 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) would indicate that the **global** missing data generating mechanism is not completely at random.

```r
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]

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

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

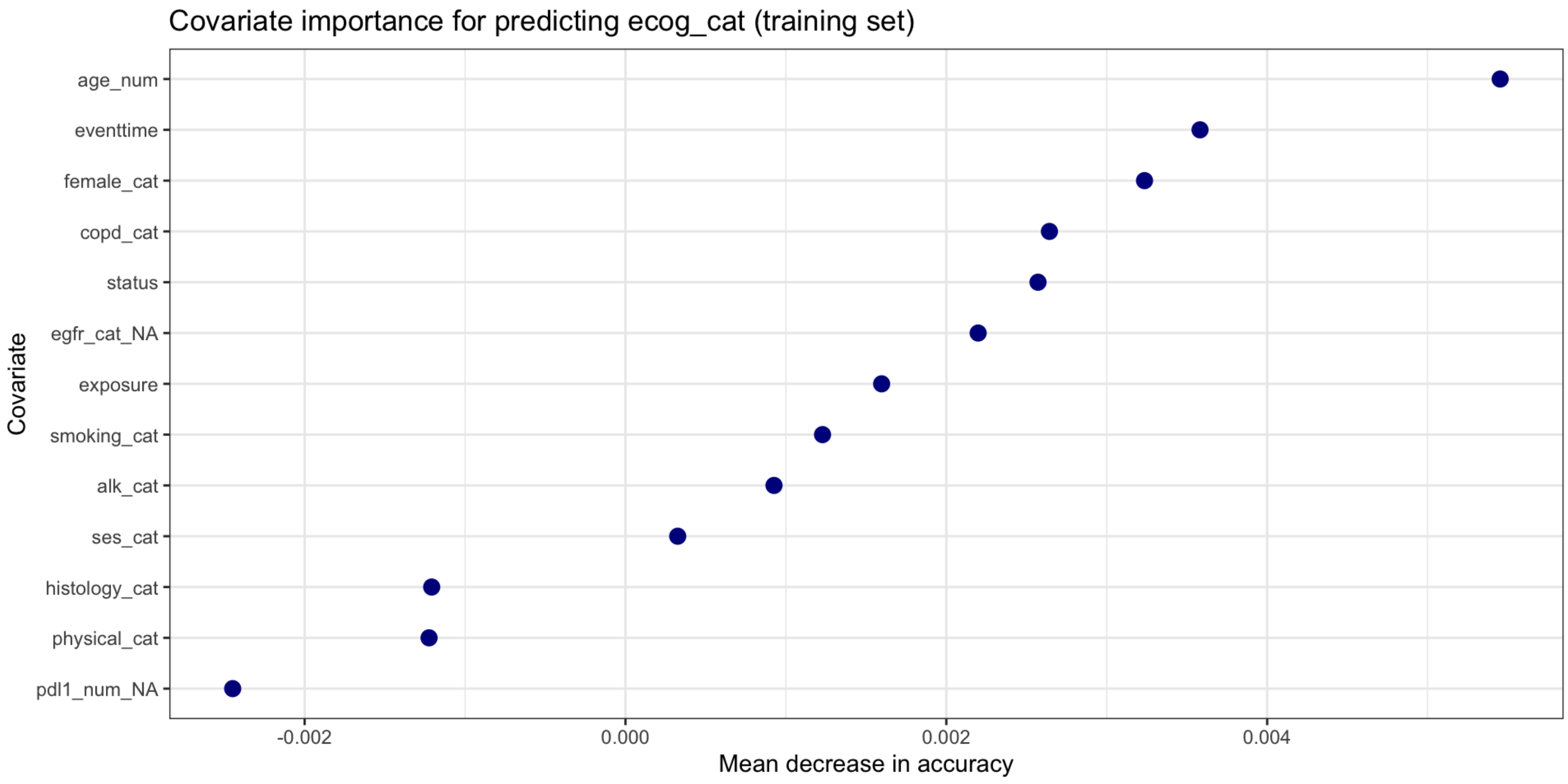
Parallelization

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.

```
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?).

```r
outcome <- smdi_outcome(
  data = smdi_data,
  model = "cox",
  form_lhs = "Surv(eventtime, status)",
  exponentiated = FALSE
  )

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

```r
diagnostics <- smdi_diagnose(
  data = smdi_data,
  model = "cox",
  form_lhs = "Surv(eventtime, status)",
  n_cores = 3
  )

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:

```r
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:

```r
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:

```r
diagnostics %>%
  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.:

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

Test it out yourself

```r
# install.packages("devtools")
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)

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References

ⓘ **References cited in this presentation**

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