Package ‘RobinCar2’

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Type Package

Title ROBust INference for Covariate Adjustment in Randomized Clinical Trials

Version 0.2.0

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Description Performs robust estimation and inference when using covariate adjustment and/or covariate-adaptive randomization in randomized controlled trials.
This package is trimmed to reduce the dependencies and validated to be used across industry.
See ``FDA's final guidance on covariate adjustment''<`https://www.regulations.gov/docket/FDA-2019-D-0934`>, Tsiatis (2008) <doi:10.1002/sim.3113>,
Bugni et al. (2018) <doi:10.1080/01621459.2017.1375934>, Ye, Shao, Yi, and Zhao (2023)<doi:10.1080/01621459.2022.2
Ye, Shao, and Yi (2022)<doi:10.1093/biomet/asab015>, Rosenblum and van der Laan (2010)<doi:10.2202/1557-4679.1138>,
Wang et al. (2021)<doi:10.1080/01621459.2021.1981338>, Ye, Bannick, Yi, and Shao (2023)<doi:10.1080/24754269.2023.2205802>,
and Bannick, Shao, Liu, Du, Yi, and Ye (2024)<doi:10.48550/arXiv.2306.10213>.

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URL `https://github.com/openpharma/RobinCar2/`

BugReports `https://github.com/openpharma/RobinCar2/issues`

Depends R (>= 3.6)

Imports checkmate, numDeriv, MASS, sandwich, stats, survival, utils

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Contents

`RobinCar2-package` `RobinCar2` *Package*

Description

`RobinCar2` implements unbiased prediction and robust inference of variance of a fit in R.

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See Also

Useful links:

- `https://github.com/openpharma/RobinCar2/`
- Report bugs at `https://github.com/openpharma/RobinCar2/issues`

`confint` *Confidence Interval*

Description

Obtain the confidence interval for the marginal mean or the contrast.

Usage

```
## S3 method for class 'prediction_cf'
confint(object, parm, level = 0.95, include_se = FALSE, ...)

## S3 method for class 'surv_effect'
confint(object, parm, level = 0.95, transform, ...)

## S3 method for class 'treatment_effect'
confint(object, parm, level = 0.95, transform, ...)
```

Arguments

`object`	Object to construct confidence interval.
`parm`	(`character` or `integer`) Names of the parameters to construct confidence interval.
`level`	(`numeric`) Confidence level.
`include_se`	(`flag`) Whether to include the standard error as a column in the result matrix.
`...`	Not used.
`transform`	(`function`) Transform function.

Value

A `matrix` of the confidence interval.

Examples

```
robin_res <- robin_glm(
  y_b ~ treatment * s1,
  data = glm_data, treatment = treatment ~ s1, contrast = "log_risk_ratio"
)
confint(robin_res$marginal_mean, level = 0.7)
confint(robin_res$contrast, parm = 1:3, level = 0.9)
```

`find_data` *Find Data in a Fit*

Description

Find Data in a Fit

Usage

```
find_data(fit, ...)
```

Arguments

`fit`	A fit object.
`...`	Additional arguments.

Value

A data frame used in the fit.

`glm_data` *Example Trial Data for GLMs with Permute-Block Randomization*

Description

This dataset contains the trial example data for GLMs with permute block randomization.

Usage

```
glm_data
```

Format

A data frame with 600 rows and 7 columns:

id The ID of the patients.

treatment The treatment assignment, "pbo", "trt1" and "trt2"

s1 The first stratification variable, "a" and "b".

s2 The second stratification variable, "c" and "d".

covar The covariate following normal distribution.

y The continuous response.

y_b The binary response.

Source

The data is generated by the `create_glm_data.R` script.

`h_diff` *Contrast Functions and Jacobians*

Description

Contrast Functions and Jacobians

Create Contrast of Pairs

Usage

```
h_diff(x, y)

h_jac_diff(x, y)

h_risk_ratio(x, y)

h_jac_risk_ratio(x, y)

h_odds_ratio(x, y)

h_jac_odds_ratio(x, y)

h_log_risk_ratio(x, y)

h_jac_log_risk_ratio(x, y)

h_log_odds_ratio(x, y)

h_jac_log_odds_ratio(x, y)

eff_jacob(f)

pairwise(levels, x = levels)

against_ref(levels, ref = levels[1], x = tail(levels, -1))

custom_contrast(levels, x, y)
```

Arguments

`x`	(`vector`) A vector of treatment levels.
`y`	(`vector`) A vector of treatment levels.
`f`	(`function`) Function with argument x and y to compute treatment effect.
`levels`	(`character`) Levels of the treatment.
`ref`	(`string` or `int`) Reference level.

Value

Vector of contrasts, or matrix of jacobians.

A list of `contrast` object with following elements:

- Index of the treatment group.
- Index of the reference group. Additional attributes include `levels` and `max_levels` indicating the names of the treatment levels and the maximum number of levels.

Examples

```
h_diff(1:3, 4:6)
h_jac_risk_ratio(1:3, 4:6)
```

`predict_counterfactual` *Counterfactual Prediction*

Description

Obtain counterfactual prediction of a fit.

Usage

```
predict_counterfactual(fit, treatment, data, vcov, vcov_args, ...)
```

Arguments

`fit`	fitted object.
`treatment`	(`formula`) formula of form treatment ~ strata(s).
`data`	(`data.frame`) raw dataset.
`vcov`	(`function` or `character`) variance function or name.
`vcov_args`	(`list`) additional arguments for variance function.
`...`	Additional arguments for methods.

Value

List of class `prediction_cf` containing following elements:

- `estimate`: predicted marginal mean.
- `residual`: residual of the bias-corrected prediction.
- `predictions`: all predicted values.
- `predictions_liner`: linear predictions.
- `schema`: randomization schema.
- `response`: response value.
- `fit`: fitted model.
- `model_matrix`: model matrix.
- `treatment_formula`: treatment assignment and randomization formula.
- `treatment`: treatment value.
- `group_idx`: group index based on the stratification.
- `variance`: estimated variance of the marginal mean.
- `variance_name`: name of the variance.

`robin_glm` *Covariate adjusted glm model*

Description

Covariate adjusted glm model

Usage

```
robin_glm(
  formula,
  data,
  treatment,
  contrast = c("difference", "risk_ratio", "odds_ratio", "log_risk_ratio",
    "log_odds_ratio"),
  contrast_jac = NULL,
  vcov = "vcovG",
  family = gaussian(),
  vcov_args = list(),
  pair,
  ...
)
```

Arguments

`formula`	(`formula`) A formula of analysis.
`data`	(`data.frame`) Input data frame.
`treatment`	(`formula` or `character(1)`) A formula of treatment assignment or assignment by stratification, or a string name of treatment assignment.
`contrast`	(`function` or `character(1)`) A function to calculate the treatment effect, or character of "difference", "risk_ratio", "odds_ratio" for default contrasts.
`contrast_jac`	(`function`) A function to calculate the Jacobian of the contrast function. Ignored if using default contrasts.
`vcov`	(`function`) A function to calculate the variance-covariance matrix of the treatment effect, including `vcovHC` and `vcovG`.
`family`	(`family`) A family object of the glm model.
`vcov_args`	(`list`) Additional arguments passed to `vcov`.
`pair`	Pairwise treatment comparison.
`...`	Additional arguments passed to `glm` or `glm.nb`.

Details

If family is `MASS::negative.binomial(NA)`, the function will use `MASS::glm.nb` instead of `glm`.

Value

A robin_output object, with `marginal_mean` and `contrast` components.

Examples

```
robin_glm(
  y ~ treatment * s1,
  data = glm_data,
  treatment = treatment ~ s1, contrast = "difference"
)
```

`robin_lm` *Covariate adjusted lm model*

Description

Covariate adjusted lm model

Usage

```
robin_lm(
  formula,
  data,
  treatment,
  vcov = "vcovG",
  vcov_args = list(),
  pair,
  ...
)
```

Arguments

`formula`	(`formula`) A formula of analysis.
`data`	(`data.frame`) Input data frame.
`treatment`	(`formula` or `character(1)`) A formula of treatment assignment or assignment by stratification, or a string name of treatment assignment.
`vcov`	(`function`) A function to calculate the variance-covariance matrix of the treatment effect, including `vcovHC` and `vcovG`. The default is 'vcovG'.
`vcov_args`	(`list`) Additional arguments passed to `vcov`.
`pair`	Pairwise treatment comparison.
`...`	Additional arguments passed to `lm`.

Value

A robin_output object, with `marginal_mean` and `contrast` components.

Examples

```
robin_lm(
  y ~ treatment * s1,
  data = glm_data,
  treatment = treatment ~ s1
)
```

`robin_surv` *Covariate Adjusted and Stratified Survival Analysis*

Description

Calculate log-rank test as well as hazard ratio estimates for survival data, optionally adjusted for covariates and a stratification factor.

Usage

```
robin_surv(
  formula,
  data,
  treatment,
  comparisons,
  contrast = "hazardratio",
  test = "logrank",
  ...
)
```

Arguments

`formula`	(`formula`) A formula of analysis, of the form `Surv(time, status)` ~ `covariates`. (If no covariates should be adjusted for, use `1` instead on the right hand side.)
`data`	(`data.frame`) Input data frame.
`treatment`	(`formula`) A formula of treatment assignment or assignment by stratification.
`comparisons`	(`list`) An optional list of comparisons between treatment levels to be performed, see details. By default, all pairwise comparisons are performed automatically.
`contrast`	(`character(1)`) The contrast statistic to be used, currently only `"hazardratio"` is supported.
`test`	(`character(1)`) The test to be used, currently only `"logrank"` is supported.
`...`	Additional arguments passed to the survival analysis functions, in particular `hr_se_plugin_adjusted` (please see here for details).

Details

The user can optionally specify a list of comparisons between treatment levels to be performed. The list must have two elements:

- Treatment level indices of the treatment group.
- Treatment level indices of the control group.

So for example if you would like to compare level 3 with level 1, and also level 3 with level 2 (but not level 2 with level 1) then you can specify: `comparisons = list(c(3, 3), c(1, 2))`

Value

A `surv_effect` object containing the results of the survival analysis.

See Also

surv_effect_methods for S3 methods.

Examples

```
# Adjusted for covariates meal.cal and age and adjusted for stratification by sex:
robin_surv(
  formula = Surv(time, status) ~ meal.cal + age,
  data = surv_data,
  treatment = sex ~ strata
)

# Adjusted for stratification by strata but not for covariates:
robin_surv(
  formula = Surv(time, status) ~ 1,
  data = surv_data,
  treatment = sex ~ strata
)

# Unadjusted for covariates and stratification:
robin_surv(
  formula = Surv(time, status) ~ 1,
  data = surv_data,
  treatment = sex ~ 1
)
```

`surv_data` *Survival Example Data*

Description

This dataset contains survival data from the `survival` package's survival::lung dataset, modified to include factors for `sex` and `strata`, as well as a binary `status` variable which is 1 for death and 0 for censored.

Usage

```
surv_data
```

Format

An object of class `data.frame` with 228 rows and 12 columns.

Source

The data is generated by the `create_surv_data.R` script.

`surv_effect_methods` *S3 Methods for* `surv_effect`

Description

S3 Methods for `surv_effect`

Usage

```
## S3 method for class 'surv_effect'
print(x, ...)

table(x, ...)

## Default S3 method:
table(x, ...)

## S3 method for class 'surv_effect'
table(x, ...)
```

Arguments

`x`	(`surv_effect`) the obtained result from `robin_surv()`.
`...`	ignored additional arguments (for compatibility).

Functions

- `print(surv_effect)`: prints the `surv_effect` object.
- `table(surv_effect)`: prints and returns invisibly the events table of the `surv_effect` object.

Examples

```
x <- robin_surv(
  formula = Surv(time, status) ~ meal.cal + age,
  data = surv_data,
  treatment = sex ~ strata
)
print(x)
table(x)
```

`treatment_effect` *Treatment Effect*

Description

Obtain treatment effect and variance from counter-factual prediction

Usage

```
treatment_effect(
  object,
  pair = pairwise(names(object$estimate)),
  eff_measure,
  eff_jacobian = eff_jacob(eff_measure),
  contrast_name,
  ...
)

difference(object, ...)

risk_ratio(object, ...)

odds_ratio(object, ...)

log_risk_ratio(object, ...)

log_odds_ratio(object, ...)
```

Arguments

`object`	Object from which to obtain treatment effect.
`pair`	(`contrast`) Contrast choices.
`eff_measure`	(`function`) Treatment effect measurement function.
`eff_jacobian`	(`function`) Treatment effect jacobian function.
`contrast_name`	(`string`) Name of the contrast.
`...`	Additional arguments for variance.

Value

A list of `treatment_effect` object with following elements:

- `estimate`: estimate of the treatment effect.
- `pair`: `contrast` object indicating the pairwise treatment effect.
- `contrast`: name of the contrast function.
- `euqal_val`: the value for no treatment effect given the contrast.
- `variance`: the variance of the treatment effect.
- `jacobian`: the Jacobian matrix.
- `contrast_mat`: contrast summary matrix.

`vcovG` *Generalized Covariance (ANHECOVA)*

Description

Generalized Covariance (ANHECOVA)

Usage

```
vcovG(x, decompose = TRUE, ...)
```

Arguments

`x`	(`prediction_cf`) Counter-factual prediction.
`decompose`	(`flag`) whether to use decompose method to calculate the variance.
`...`	Not used.

Value

Named covariance matrix.

`vcovHC` *Heteroskedasticity-consistent covariance matrix for predictions*

Description

The heteroskedasticity-consistent covariance matrix for predictions is obtained with `sandwich::vocvHC` using sandwich method.

Usage

```
vcovHC(x, type = "HC3", ...)
```

Arguments

`x`	(`prediction_cf`) Counter-factual prediction.
`type`	(`character`) Type of HC covariance matrix.
`...`	Additional arguments for `sandwich::vcovHC`.

Value

Matrix of the heteroskedasticity-consistent covariance for the predictions.

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