Package ‘pseval’

January 28, 2019

Type Package
Title Methods for Evaluating Principal Surrogates of Treatment Response
Version 1.3.1
Date 2019-01-10
Maintainer Michael C Sachs <sachsmc@gmail.com>
Description Contains the core methods for the evaluation of principal surrogates in a single clinical trial. Provides a flexible interface for defining models for the risk given treatment and the surrogate, the models for integration over the missing counterfactual surrogate responses, and the estimation methods. Estimated maximum likelihood and pseudo-score can be used for estimation, and the bootstrap for inference. A variety of post-estimation summary methods are provided, including print, summary, plot, and testing.
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LazyData TRUE
Suggests ggplot2, testthat, knitr, printr, rmarkdown
Imports survival
VignetteBuilder knitr
RoxygenNote 6.1.1
NeedsCompilation no
Author Michael C Sachs [aut, cre],
      Erin E Gabriel [aut]
Repository CRAN
Date/Publication 2019-01-28 07:40:03 UTC

R topics documented:

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### Description

This operator allows you to add objects to a psdesign object, such as integration models and risk models.

### Usage

```r
## S3 method for class 'ps'
p1 + p2
```
**add_bootstrap**

**Arguments**

- **p1** An object of class `psdesign`
- **p2** Another object to be added to p1, see list below for possible options

If the first object is an object of class `psdesign`, you can add the following types of objects, and it will return a modified `psdesign` object. Users will generally add them in the order that they appear.

- **integration**: Add or replace integration model
- **riskmodel**: Add or replace risk model
- **estimate**: Estimate parameters
- **bootstrap**: Bootstrap estimates

---

**add_bootstrap**

Bootstrapping parameters

**Description**

Bootstrap resampling parameters

**Usage**

```r
add_bootstrap(psdesign, bootstrap)
```

**Arguments**

- **psdesign** A `psdesign` object, it must have risk model and integration model components
- **bootstrap** A bootstrap object created by `ps_bootstrap`

**Examples**

```r
## Not run:
test <- psdesign(generate_example_data(n = 100), Z = Z, Y = Y.obs, S = S.obs, BIP = BIP)
est1 <- test + integrate_parametric(S.1 ~ BIP) + risk_binary() + ps_estimate(method = "BFGS")
est1 + ps_bootstrap(method = "BFGS", start = est1$estimates$par, n.boots = 50)
## End(Not run)
```
add_estimate

Description
Estimate parameters

Usage
add_estimate(psdesign, estimate)

Arguments
- psdesign: A psdesign object, it must have risk model and integration model components
- estimate: An estimate object created by ps_estimate

Examples
test <- psdesign(generate_example_data(n = 100), Z = Z, Y = Y.obs, S = S.obs, BIP = BIP)
test + integrate_parametric(S.1 ~ BIP) + risk_binary(D = 50) + ps_estimate(method = "BFGS")

add_integration

Description
Add integration model to a psdesign object

Usage
add_integration(psdesign, integration)

Arguments
- psdesign: A psdesign object
- integration: An integration object
Details

This is a list of the available integration models. The fundamental problem in surrogate evaluation is that there are unobserved values of the counterfactual surrogate responses $S(1)$. In the estimated maximum likelihood framework, for subjects missing the $S(1)$ values, we use an auxiliary pre-treatment variable or set of variables $W$ that is observed for every subject to estimate the distribution of $S(1) | W$. Typically, this $W$ is a BIP. Then for each missing $S(1)$, we integrate likelihood contributions over each non-missing $S(1)$ given their value of $W$, and average over the contributions.

- **integrate_parametric** This is a parametric integration model that fits a linear model for the mean of $S(1) | W$ and assumes a Gaussian distribution.
- **integrate_bivnorm** This is another parametric integration model that assumes that $S(1)$ and $W$ are jointly normally distributed. The user must specify their mean, variances and correlation.
- **integrate_nonparametric** This is a non-parametric integration model that is only valid for categorical $S(1)$ and $W$. It uses the observed proportions to estimate the joint distribution of $S(1), W$.
- **integrate_semiparametric** This is a semi-parametric model that uses the semi-parametric location scale model of Heagerty and Pepe (1999). Models are specified for the location of $S(1) | W$ and the scale of $S(1) | W$. Then integrations are drawn from the empirical distribution of the residuals from that model, which are then transformed to the appropriate location and scale.

Examples

```r
test <- psdesign(generate_example_data(n = 100), Z = Z, Y = Y.obs, S = S.obs, BIP = BIP)
add_integration(test, integrate_parametric(S.1 ~ BIP))
test + integrate_parametric(S.1 ~ BIP)  # same as above
```

---

**add_riskmodel**

Add risk model to a psdesign object

Description

Add risk model to a psdesign object

Usage

```r
add_riskmodel(psdesign, riskmodel)
```

Arguments

- **psdesign** A psdesign object
- **riskmodel** A risk model object, from the list above
Details

The risk model component specifies the likelihood for the data. This involves specifying the distribution of the outcome variable, whether it is binary or time-to-event, and specifying how the surrogate S(1) and the treatment Z interact and affect the outcome. We use the formula notation to be consistent with other regression type models in R. Below is a list of available risk models.

- **risk_binary** This is a generic risk model for binary outcomes. The user can specify the formula, and link function using either `risk.logit` for the logistic link, or `risk.probit` for the probit link. Custom link functions may also be specified, which take a single numeric vector argument, and returns a vector of corresponding probabilities.
- **risk_weibull** This is a parameterization of the Weibull model for time-to-event outcomes that is consistent with that of `rweibull`. The user specifies the formula for the linear predictor of the scale parameter.
- **risk_exponential** This is a simple exponential model for a time-to-event outcome.
- **risk_poisson** This is a Poisson model for count outcomes. It allows for offsets in the formula.
- **risk_continuous** This is a Gaussian model for continuous outcomes. It assumes that larger values of the outcome are harmful (e.g. blood pressure)

Examples

```r
test <- psdesign(generate_example_data(n = 100), Z = Z, Y = Y.obs, S = S.obs, BIP = BIP) + integrate_parametric(S.1 ~ BIP)
add_riskmodel(test, risk_binary())
test + risk_binary() # same as above
```

calc_risk Calculate the risk and functions of the risk

Description

Computes the treatment efficacy (TE) and other functions of the risk in each treatment arm over the range of surrogate values observed in the data. TE(s) is defined as \(1 - \frac{\text{risk}(s, z = 1)}{\text{risk}(s, z = 0)}\), where \(z\) is the treatment indicator. If any other variables are present in the risk model, then the risk is computed at their median value.

Usage

calc_risk(psdesign, contrast = "TE", t, sig.level = 0.05, 
CI.type = "band", n.samps = 5000, bootstraps = TRUE, 
newdata = NULL)
calc_risk

Arguments

psdesign A psdesign object. It must contain a risk model, an integration model, and estimated parameters. Bootstrapped parameters are optional

contrast The contrast function, or the name of the contrast function. See details.

t For time to event outcomes, a fixed time t may be provided to compute the cumulative distribution function. If not, the restricted mean survival time is used. Omit for binary outcomes.

sig.level Significance level for bootstrap confidence intervals

CI.type Character string, "pointwise" for pointwise confidence intervals, and "band" for simultaneous confidence band.

n.samps The number of samples to take over the range of S.1 at which the contrast is calculated

bootstraps If true, and bootstrapped estimates are present, will calculate bootstrap standard errors and confidence bands.

newdata Vector of S values. If present, will calculate the contrast function at values of newdata instead of the observed S.1

Details

The contrast function is a function that takes 2 inputs, the risk_0 and risk_1, and returns some one dimensional function of those two inputs. It must be vectorized. Some built-in functions are "TE" for treatment efficacy = 1 - risk_1(s)/risk_0(s), "RR" for relative risk = risk_1(s)/risk_0(s), "logRR" for log of the relative risk, and "RD" for the risk difference = risk_1(s) - risk_0(s).

Value

A data frame containing columns for the S values, the computed contrast function at S, R0, and R1 at those S values, and optionally standard errors and confidence intervals computed using bootstrapped estimates.

Examples

## Not run:
# same result passing function name or function
calc_risk(binary.boot, contrast = "TE", n.samps = 20)
calc_risk(binary.boot, contrast = function(R0, R1) 1 - R1/R0, n.samps = 20)

## End(Not run)
calc_STG  

*Calculate the Standardized total gain*

**Description**

Computes the standardized total gain for the risk difference. Optionally produces bootstrap standard errors and confidence intervals. The standardized total gain is the area between the risk difference curve and the horizontal line at the marginal risk difference. If the outcome is time to event then the STG is time-dependent, and a time point for evaluation is needed. If one is not provided then the restricted mean survival is estimated from the data and used.

**Usage**

```r
calc_STG(psdesign, t, sig.level = 0.05, n.samps = 5000, 
          bootstraps = TRUE, permute = TRUE, permute.times = 2000, 
          progress.bar = TRUE)
```

**Arguments**

- `psdesign`: A psdesign object. It must contain a risk model, an integration model, and estimated parameters. Bootstrapped parameters are optional.
- `t`: For time to event outcomes, a fixed time \( t \) may be provided to compute the cumulative distribution function. If not, the restricted mean survival time is used. Omit for binary outcomes.
- `sig.level`: Significance level for bootstrap confidence intervals. Omit for binary outcomes.
- `n.samps`: The number of samples to take over the range of \( S_1 \) at which the VE is calculated.
- `bootstraps`: If true, and bootstrapped estimates are present, will calculate bootstrap standard errors and confidence interval.
- `permute`: Not used, included for backwards compatibility.
- `permute.times`: Not used, included for backwards compatibility.
- `progress.bar`: Not used, included for backwards compatibility.

empirical_TE  

*Compute the empirical Treatment Efficacy*

**Description**

Compute the empirical Treatment Efficacy.

**Usage**

```r
demirical_TE(psdesign, t)
```
empirical_VE

Arguments

- `psdesign` An object of class `psdesign`
- `t` Fixed time for time to event outcomes to compute TE. If missing, uses restricted mean survival.

Description

Included for backwards compatibility

Usage

`empirical_VE(psdesign, t)`

Arguments

- `psdesign` An object of class `psdesign`
- `t` Fixed time for time to event outcomes to compute TE. If missing, uses restricted mean survival.

expand_augdata

Description

Expand augmented data using the integration function

Usage

`expand_augdata(model, psdesign, D = 500)`

Arguments

- `model` Formula defining the risk model
- `psdesign` An object of class `psdesign`, that contains at least 1 integration model
- `D` The number of samples to take for the simulated annealing
generate_example_data  
*Generate sample data used for testing*

**Description**

Generate sample data used for testing

**Usage**

```r
generate_example_data(n)
```

**Arguments**

- `n`: Integer, the sample size

integrate_bivnorm  
*Bivariate normal integration models for the missing S(1)*

**Description**

This model assumes that the pair \([S(1), W]\) is bivariate normal, where \(W\) is the BIP. The means, standard deviations, and correlation are estimated or fixed before calling this function. Then the conditional normal formula is applied in order to get the distribution of \(S(1) | W\). That distribution is used to integrate over the missing \(S(1)\) values. This method requires a BIP in the design.

**Usage**

```r
integrate_bivnorm(x = "S.1", mu = c(0, 0), sd = c(1, 1), rho = 0.2)
```

**Arguments**

- `x`: expression identifying the variable to be integrated. Typically this is \(S.1\) or \(S.0\)
- `mu`: means of the pair of surrogates, missing one first
- `sd`: standard deviations of the pair, missing one first
- `rho`: the correlation between \(X1\) and \(X2\)
**integrate_nonparametric**

*Nonparametric integration model for the missing S(1)*

**Description**

Both S(1) and the BIP or set of BIPs must be categorical. This model integrates over the estimated distribution of $S(1) | \text{BIP}$

**Usage**

```r
integrate_nonparametric(formula, ...)  
```

**Arguments**

- **formula**
  - Formula specifying the integration model for the surrogate under treatment. Generally the candidate surrogate will be on the left side in the formula, and the BIP or BIPs will be on the right side. In this case the BIP and the $S(1)$ must be categorical.

- **...**
  - Not currently used

**integrate_parametric**

*Parametric integration model for the missing S(1)*

**Description**

Parametric integration model for the missing $S(1)$

**Usage**

```r
integrate_parametric(formula, family = gaussian, ...)  
```

**Arguments**

- **formula**
  - Formula specifying the integration model for the surrogate under treatment. Generally the candidate surrogate will be on the left side in the formula, and the BIP or BIPs will be on the right side

- **family**
  - Assumed distribution for the integration model. Must be compatible with the `family` argument of `glm`. Currently only Gaussian models are supported

- **...**
  - Arguments passed to `glm`
integrate_semiparametric

Semiparametric integration model using the location-scale model

**Description**

Semiparametric integration model using the location-scale model

**Usage**

```r
integrate_semiparametric(formula.location, formula.scale, ...)
```

**Arguments**

- `formula.location`  
  Formula specifying the integration model for the location component of the surrogate under treatment. Generally the candidate surrogate will be on the left side in the formula, and the BIP or BIPs will be on the right side

- `formula.scale`  
  Formula specifying the integration model for the scale component of the surrogate under treatment. Generally the candidate surrogate will be on the left side in the formula, and the BIP or BIPs will be on the right side

- `...`  
  Other parameters passed to `sp_locscale`

---

**plot.psdesign**

*Plot summary statistics for a psdesign object*

**Description**

Plot the treatment efficacy or another contrast of risk versus S.1 for an estimated psdesign object

**Usage**

```r
## S3 method for class 'psdesign'
plot(x, t, contrast = "TE", sig.level = 0.05,
     CI.type = "band", n.samps = 500, xlab = "S.1", ylab = contrast,
     col = 1, lty = 1, lwd = 1, ...)
```

**Arguments**

- `x`  
  A `psdesign` object that contains a risk model, integration model, and valid estimates

- `t`  
  For time to event outcomes, a fixed time `t` may be provided to compute the cumulative distribution function. If not, the restricted mean survival time is used. Omit for binary outcomes.
contrast Name of contrast function to plot. "TE" or "VE" for treatment (vaccine) efficacy = 1 - risk_1(s)/risk_0(s), "RR" for relative risk = risk_1(s)/risk_0(s), "logRR" for log of the relative risk, "risk" for the risk in each treatment arm, and "RD" for the risk difference = risk_1(s) - risk_0(s). You can also pass a custom function directly as long as it takes 2 vectors as input (risk0 and risk1) and returns 1 vector of the same length.

sig.level Significance level used for confidence bands on the contrast curve. This is only used if bootstrapped estimates are available.

CI.type Character string, "pointwise" for pointwise confidence intervals, and "band" for simultaneous confidence band.

n.samps Number of samples to use over the range of S.1 for plotting the curve

xlab X-axis label

ylab Y-axis label

col Vector of integers specifying colors for each curve.

lty Vector of integers specifying linetypes for each curve.

lwd Vector of numeric values for line widths.

... Other arguments passed to plot

---

print.psdesign

Concisely print information about a psdesign object

Description

Concisely print information about a psdesign object

Usage

```r
## S3 method for class 'psdesign'
print(x, digits = 3, sig.level = 0.05, ...)
```

Arguments

- `x` An object of class psdesign
- `digits` Number of significant digits to display
- `sig.level` Significance level to use for computing bootstrapped confidence intervals
- `...` Currently unused
**psdesign**  
*Specify a design for a principal surrogate evaluation*

**Description**

Generate mappings that describe how variables in the data are mapped to components of the principal surrogate analysis. Other than data, this is a list of key-value pairs describing the common elements of a ps analysis. The required keys are Z, Y, and S. Optional keys are BIP, CPV, BSM, and weights. These elements are described in details below. Additional keys-value pairs can be included in ... This function generates an augmented dataset and additional information for subsequent steps in the analysis. In the subsequent steps, refer to the variables by the keys. See add_integration and add_riskmodel for information on how to proceed in the analysis.

**Usage**

```r
psdesign(data, Z, Y, S, BIP = NULL, CPV = NULL, BSM = NULL, weights = NULL, tau, ...)
```

**Arguments**

- `data` Data frame containing data to be analyzed
- `Z` Expression defining the treatment variable which has 2 levels
- `Y` Expression defining the outcome variable. For binary events this should be coded as 0/1 or a factor with 2 levels. For censored time-to-event outcomes this can be a call to `Surv`
- `S` Expression defining the candidate surrogate
- `BIP` Optional expression defining the baseline irrelevant predictor
- `CPV` Optional expression defining the closeout placebo vaccination measurement
- `BSM` Optional expression defining the baseline surrogate measurement
- `weights` optional expression defining weights to accommodate nonrandom subsampling, such as case control or two phase
- `tau` numeric, When the outcome Y is a survival time, it is possible that the surrogate was measured at some time tau after enrollment. Use the argument tau to specify the time when the surrogate was measured, in study time. Not required for binary Y.
- `...` Other key-value pairs that will be included in the augmented data, e.g. additional candidate surrogates, covariates for adjustment, variables used for integration
pseudo_score

Estimate parameters from a specified model using pseudo-score

Description

Estimate parameters from a specified model using pseudo-score

Usage

pseudo_score(psdesign, start = NULL, epsilon = 1e-05, maxit = 50)

Arguments

psdesign An object of class psdesign
start Vector of starting values, if NULL, will come up with starting values
epsilon Convergence criteria
maxit Maximum number of iterations

ps_bootstrap

Estimate parameters from a specified model using bootstrap resampling and estimated maximum likelihood

Description

Estimate parameters from a specified model using bootstrap resampling and estimated maximum likelihood

Usage

ps_bootstrap(n.boots = 200, progress.bar = TRUE, start = NULL, method = "BFGS", control = list(), ...)

Arguments

n.boots Number of bootstrap replicates
progress.bar Logical, if true will display a progress bar in the console
start Vector of starting values, if NULL, will come up with starting values
method Method to use for optimization, can be "pseudo-score" for categorical S with nonparametric integration, or any of the methods available in optim. Defaults to "BFGS"
control List of control parameters for passed to optim
... Arguments passed to optim
**ps_estimate**

*Estimate parameters from a specified model using estimated maximum likelihood*

**Description**

Estimate parameters from a specified model using estimated maximum likelihood

**Usage**

```r
ps_estimate(start = NULL, method = "BFGS", control = list(), ...)
```

**Arguments**

- **start** Vector of starting values, if NULL, will come up with starting values
- **method** Method to use for optimization, can be "pseudo-score" for categorical BIP, or any of the methods available in `optim`. Defaults to "BFGS"
- **control** List of control parameters for passed to `optim`
- **...** Arguments passed to `optim` or `pseudo_score`.

**risk.logit**

*Logit link function*

**Description**

Logit link function

**Usage**

```r
risk.logit(x)
```

**Arguments**

- **x** A vector of linear predictors

**Value**

A vector of probabilities
**risk.probit**

Probit link function

**Description**
Probit link function

**Usage**
risk.probit(x)

**Arguments**

- x: A vector of linear predictors

**Value**
A vector of probabilities

---

**riskcalc**

Calculate risks with handlers for survival data

**Description**
Calculate risks with handlers for survival data

**Usage**
riskcalc(risk.function, Y, par, t, dat0, dat1)

**Arguments**

- risk.function: Function taking three arguments, a data.frame, parameters, and time. It should return a vector the same number of rows as the data frame
- Y: The outcome variable
- par: the vector of parameter values
- t: Time for a survival outcome, may be missing
- dat0: Data frame containing S and Z = 1
- dat1: Data frame containing S and Z = 0
**risk_binary**

*Risk model for binary outcome*

**Description**

Risk model for binary outcome

**Usage**

```
risk_binary(model = Y ~ S.1 * Z, D = 5000, risk = risk.logit)
```

**Arguments**

- **model**: Formula specifying the risk model
- **D**: number of samples for the simulated annealing integration
- **risk**: Function for transforming a linear predictor into a probability. E.g., `risk.logit` for the logistic model, `risk.probit` for the probit model

---

**risk_continuous**

*Risk model for continuous outcome*

**Description**

This model assumes that the outcome Y is normally distributed conditional on S.1 and Z, with mean determined by the model formula. It also assumes that larger values of Y are more indicative of poor outcomes, e.g., blood pressure.

**Usage**

```
risk_continuous(model = Y ~ S.1 * Z, D = 5000)
```

**Arguments**

- **model**: Formula specifying the risk model for the mean
- **D**: number of samples for the simulated annealing integration
risk_exponential  

**Exponential risk model for time to event outcome**

**Description**

Exponential risk model for time to event outcome

**Usage**

```r
risk_exponential(model = Y ~ S.1 * Z, D = 5000)
```

**Arguments**

- `model`: Formula specifying the risk model. The outcome should be a `Surv` object specifying right censoring.
- `D`: number of samples for simulated annealing

---

risk_poisson  

**Poisson risk model for count outcomes**

**Description**

Poisson risk model for count outcomes

**Usage**

```r
risk_poisson(model = Y ~ S.1 * Z, D = 5000)
```

**Arguments**

- `model`: Formula specifying the risk model. The outcome should be an integer of counts. This right side of the formula may contain an offset term.
- `D`: number of samples for simulated annealing
risk_weibull  

Weibull risk model for time to event outcome

Description

Weibull risk model for time to event outcome

Usage

risk_weibull(model = Y ~ S.1 * Z, D = 5000)

Arguments

model  
Formula specifying the risk model. The outcome should be a Surv object specifying right censoring

D  
number of samples for simulated annealing

sp_locscale  

Fit the semi-parametric location-scale model

Description

This estimates the location-scale model as described in Heagerty and Pepe (1999) using the Newton-Raphson method. The location and scale formulas must have the same outcome, but they may have different predictors.

Usage

sp_locscale(formula.location, formula.scale, data, weights, tol = 1e-06, maxit = 100)

Arguments

formula.location  
Formula specifying the model for the location

formula.scale  
Formula specifying the model for the scale

data  
Data used to estimate the model

weights  
Weights applied to the estimating equations

tol  
Convergence tolerance

maxit  
Maximum number of iterations

Value

A list containing the parameter estimates, the convergence indicator, and residuals
stg

*Compute the standardized total gain*

**Description**

Compute the standardized total gain

**Usage**

```
stg(R1, R0, stand = TRUE)
```

**Arguments**

- `R1`: Risk in the treatment group
- `R0`: Risk in the control group
- `stand`: Standardize?

**summarize_bs**

*Summarize bootstrap samples*

**Description**

Summarize bootstrap samples

**Usage**

```
summarize_bs(bootdf, estdf = NULL, sig.level = 0.05, CI.type = "band")
```

**Arguments**

- `bootdf`: Data frame containing bootstrapped estimates, with a column containing a convergence indicator
- `estdf`: Data frame containing full sample estimate
- `sig.level`: Significance level to use for confidence intervals
- `CI.type`: Character string, "pointwise" for pointwise confidence intervals, and "band" for simultaneous confidence band.
summary.psdesign  

Summary method for psdesign objects

Description

Summary method for psdesign objects

Usage

## S3 method for class 'psdesign'
summary(object, digits = 3, sig.level = 0.05, ...)

Arguments

- **object**: An object of class `psdesign`
- **digits**: Number of significant digits to display
- **sig.level**: Significance level to use for computing bootstrapped confidence intervals
- **...**: Currently unused

Value

Invisibly returns the printed table, along with the three estimates of vaccine efficacy. The empirical TE is 1 minus the relative risk comparing the treatment arm to the control arm. The risk is estimated as the proportion in the binary outcome case, or with the Kaplan-Meier estimate at the restricted mean survival in the time-to-event case. The marginal TE estimate is the TE estimate under the specified parametric risk model, ignoring the effect of S.1. The model based average TE is the TE estimate from the specified risk model, averaged over the distribution of S.1. The point of displaying these three is to assess the validity of the parametric model, and to assess the validity of the model estimation. Wild differences among these estimates may indicate problems with the model or convergence.

TE  

Treatment efficacy contrast functions

Description

Treatment efficacy contrast functions

Usage

TE(R0, R1)

Arguments

- **R0**: A vector of risks in the control arm
- **R1**: A vector of risks in the treatment arm
Details

These functions take the risk in the two treatment arms, and computes a one-dimensional summary of those risks. Built-in choices are "TE" for treatment efficacy = 1 - risk_1(s)/risk_0(s), "RR" for relative risk = risk_0(s)/risk_1(s), "logRR" for log of the relative risk, and "RD" for the risk difference = risk_0(s) - risk_1(s).

Value

A vector the same length as R0 and R1.

---

\begin{verbatim}
verify_trt

Check that a variable is suitable for using as binary treatment indicator
\end{verbatim}

Description

Checks for two classes and gives a warning message indicating which level is assumed to be 0/1

Usage

verify_trt(D)

Arguments

D Vector that will be checked for 2-class labels

\begin{verbatim}
wem_test

Test for wide effect modification
\end{verbatim}

Description

This runs a multivariate Wald test on the interaction terms of the model, using the bootstrap covariance

Usage

wem_test(x)

Arguments

x An object of class psdesign with bootstrap replicates
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