# Package 'stdReg2'

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<span id="page-0-0"></span>Type Package

Title Regression Standardization for Causal Inference

Version 1.0.1

URL <https://sachsmc.github.io/stdReg2/>

#### BugReports <https://github.com/sachsmc/stdReg2/issues/>

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Description Contains more modern tools for causal inference using regression standardization. Four general classes of models are implemented; generalized linear models, conditional generalized estimating equation models, Cox proportional hazards models, and shared frailty gamma-Weibull models. Methodological details are described in Sjölander, A. (2016) [<doi:10.1007/s10654-016-0157-3>](https://doi.org/10.1007/s10654-016-0157-3). Also includes functionality for doubly robust estimation for generalized linear models in some special cases, and the ability to implement custom models.

License AGPL  $(>= 3)$ 

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Suggests causaldata, AF, knitr, nnet, rmarkdown, testthat (>= 3.0.0)

VignetteBuilder knitr

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stdReg2-package *stdReg2: Regression Standardization for Causal Inference*

#### Description

Contains more modern tools for causal inference using regression standardization. Four general classes of models are implemented; generalized linear models, conditional generalized estimating equation models, Cox proportional hazards models, and shared frailty gamma-Weibull models. Methodological details are described in Sjölander, A. (2016) [doi:10.1007/s1065401601573.](https://doi.org/10.1007/s10654-016-0157-3) Also includes functionality for doubly robust estimation for generalized linear models in some special cases, and the ability to implement custom models.

# Author(s)

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- Johan Sebastian Ohlendorff
- Adam Brand

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# See Also

Useful links:

- <https://sachsmc.github.io/stdReg2/>
- Report bugs at <https://github.com/sachsmc/stdReg2/issues/>

<span id="page-2-1"></span>parfrailty *Fits shared frailty gamma-Weibull models*

#### **Description**

parfrailty fits shared frailty gamma-Weibull models. It is specifically designed to work with the function standardize\_parfrailty, which performs regression standardization in shared frailty gamma-Weibull models.

#### Usage

parfrailty(formula, data, clusterid, init)

#### Arguments



#### Details

parfrailty fits the shared frailty gamma-Weibull model

$$
\lambda(t_{ij}|C_{ij}) = \lambda(t_{ij}; \alpha, \eta) U_i \exp\{h(C_{ij}; \beta)\},
$$

where  $t_{ij}$  and  $C_{ij}$  are the survival time and covariate vector for subject j in cluster i, respectively.  $\lambda(t; \alpha, \eta)$  is the Weibull baseline hazard function

$$
\eta t^{\eta-1} \alpha^{-\eta},
$$

where  $\eta$  is the shape parameter and  $\alpha$  is the scale parameter.  $U_i$  is the unobserved frailty term for cluster i, which is assumed to have a gamma distribution with scale =  $1/\text{shape} = \phi$ .  $h(X;\beta)$  is the regression function as specified by the formula argument, parameterized by a vector  $\beta$ . The ML estimates  $\{\log(\hat{\alpha}), \log(\hat{\eta}), \log(\hat{\phi}), \hat{\beta}\}$  are obtained by maximizing the marginal (over U) likelihood.

# Value

An object of class "parfrailty" which is a list containing:



If left truncation is present, it is assumed that it is strong left truncation. This means that even if the truncation time may be subject-specific, the whole cluster is unobserved if at least one subject in the cluster dies before his/her truncation time. If all subjects in the cluster survive beyond their subject-specific truncation times, then the whole cluster is observed (Van den Berg and Drepper, 2016).

# Author(s)

Arvid Sjölander and Elisabeth Dahlqwist.

#### References

Dahlqwist E., Pawitan Y., Sjölander A. (2019). Regression standardization and attributable fraction estimation with between-within frailty models for clustered survival data. *Statistical Methods in Medical Research* 28(2), 462-485.

Van den Berg G.J., Drepper B. (2016). Inference for shared frailty survival models with lefttruncated data. *Econometric Reviews*, 35(6), 1075-1098.

# Examples

```
require(survival)
# simulate data
set.seed(5)
n < -200m \leq -3alpha <-1.5eta <- 1
phi < -0.5beta <-1id \leq rep(1:n, each = m)
U \leftarrow \text{rep}(\text{rgamma}(n, \text{ shape} = 1 / \text{phi}, \text{scale} = \text{phi}), \text{each} = \text{m})X \leq -rnorm(n * m)# reparameterize scale as in rweibull function
weibull.scale <- alpha / (U * exp(beta * X))^(1 / eta)T <- rweibull(n \times m, shape = eta, scale = weibull.scale)
# right censoring
C \le runif(n * m, 0, 10)
D \le - as.numeric(T \le C)
T \leftarrow pmin(T, C)# strong left-truncation
L \le runif(n * m, 0, 2)
incl \leq T > L
incl \leq -</math> ave(x = incl, id, FUN = sum) == mdd <- data.frame(L, T, D, X, id)
dd <- dd[incl, ]
```
# Note

# <span id="page-4-0"></span>plot.std\_glm 5

```
fit \le parfrailty(formula = Surv(L, T, D) \sim X, data = dd, clusterid = "id")
print(fit)
```
plot.std\_glm *Plots regression standardization fit*

# Description

This is a plot method for class "std\_glm".

### Usage

```
## S3 method for class 'std_glm'
plot(
 x,
 plot_ci = TRUE,
 ci_type = "plain",
 ci\_level = 0.95,
 transform = NULL,
 contrast = NULL,
  reference = NULL,
 summary_fun = "summary_std_glm",
  ...
\mathcal{L}
```
# Arguments



# Value

None. Creates a plot as a side effect

# <span id="page-5-0"></span>Examples

# see standardize\_glm

plot.std\_surv *Plots regression standardization fit*

# Description

This is a plot method for class "std\_surv".

# Usage

```
## S3 method for class 'std_surv'
plot(
  x,
  plot_ci = TRUE,
  ci_type = "plain",
  ci\_level = 0.95,
  transform = NULL,
  contrast = NULL,
  reference = NULL,
  legendpos = "bottomleft",
  summary_fun = "summary_std_coxph",
  ...
\mathcal{L}
```
# Arguments



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# Value

None. Creates a plot as a side effect

print.std\_surv *Prints summary of regression standardization fit*

# Description

Prints summary of regression standardization fit

# Usage

## S3 method for class 'std\_surv'  $print(x, \ldots)$ ## S3 method for class 'std\_glm'  $print(x, \ldots)$ ## S3 method for class 'std\_custom'

 $print(x, \ldots)$ 

#### Arguments



# Value

The object being printed, invisibly.

print.summary.parfrailty

*Print method for parametric frailty fits*

# Description

Print method for parametric frailty fits

# Usage

```
## S3 method for class 'summary.parfrailty'
print(x, digits = max(3L, getOption("digits") - 3L), ...)
```
#### <span id="page-7-0"></span>8 sandwich is a series of the series of

# Arguments



# Value

The object being printed, invisibly



# Description

Compute the sandwich variance components from a model fit

# Usage

```
sandwich(fit, data, weights, t, fit.detail)
```
# Arguments



# Value

A list consisting of the Fisher information matrix (I) and the Score equations (U)

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Get standardized estimates using the g-formula with a custom model

# Usage

```
standardize(
  fitter,
  arguments,
 predict_fun,
 data,
 values,
 B = NULL,ci\_level = 0.95,
 contrasts = NULL,
  reference = NULL,
  seed = NULL,
  times = NULL,
  transforms = NULL,
 progressbar = TRUE
)
```
#### Arguments



10 standardize



# Details

Let  $Y$ ,  $X$ , and  $Z$  be the outcome, the exposure, and a vector of covariates, respectively. standardize uses a model to estimate the standardized mean  $\theta(x) = E\{E(Y|X=x,Z)\}\,$ , where x is a specific value of  $X$ , and the outer expectation is over the marginal distribution of  $Z$ . With survival data,  $Y = I(T > t)$ , and a vector of different time points times (t) can be given, where T is the uncensored survival time.

#### Value

An object of class std\_custom. This is a list with components estimates and fit for the outcome model.

#### References

Rothman K.J., Greenland S., Lash T.L. (2008). *Modern Epidemiology*, 3rd edition. Lippincott, Williams & Wilkins.

Sjölander A. (2016). Regression standardization with the R-package stdReg. *European Journal of Epidemiology* 31(6), 563-574.

Sjölander A. (2016). Estimation of causal effect measures with the R-package stdReg. *European Journal of Epidemiology* 33(9), 847-858.

```
set.seed(6)
n < -100Z \leftarrow \text{norm}(n)X \leq -rnorm(n, mean = Z)Y \le - rbinom(n, 1, prob = (1 + \exp(X + Z))^(-1))
dd <- data.frame(Z, X, Y)
prob_predict.glm <- function(...) predict.glm(..., type = "response")
x <- standardize(
  fitter = "glm",
  arguments = list(
    formula = Y \sim X * Z,
    family = "binomial"
  ),
  predict_fun = prob_predict.glm,
  data = dd,values = list(X = seq(-1, 1, 0.1)),
```
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```
B = 100,
  reference = 0,
  contrasts = "difference"
)
x
require(survival)
prob_predict.coxph <- function(object, newdata, times) {
  fit.detail <- suppressWarnings(basehaz(object))
 cum.haz <- fit.detail$hazard[sapply(times, function(x) max(which(fit.detail$time <= x)))]
  predX <- predict(object = object, newdata = newdata, type = "risk")
  res <- matrix(NA, ncol = length(times), nrow = length(predX))
  for (ti in seq_len(length(times))) {
    res[, ti] <- exp(-predX * cum.haz[ti])
  }
  res
}
set.seed(68)
n <- 500
Z \leq -rnorm(n)X \leq -rnorm(n, mean = Z)T \leq - rexp(n, rate = exp(X + Z + X * Z)) # survival time
C <- r \exp(n, r \text{ate} = \exp(X + Z + X + Z)) # censoring time
U \leq pmin(T, C) # time at risk
D \le - as.numeric(T < C) # event indicator
dd <- data.frame(Z, X, U, D)
x <- standardize(
fitter = "coxph",
  arguments = list(
    formula = Surv(U, D) ~ X + Z + X * Z,
    method = "breslow",
    x = TRUE,y = TRUE),
  predict_fun = prob_predict.coxph,
  data = dd,times = 1:5,
  values = list(X = c(-1, 0, 1)),B = 100,
  reference = 0,
  contrasts = "difference"
)
x
```
standardize\_coxph *Regression standardization in Cox proportional hazards models*

#### Description

standardize\_coxph performs regression standardization in Cox proportional hazards models at specified values of the exposure over the sample covariate distribution. Let  $T$ ,  $X$ , and  $Z$  be the survival outcome, the exposure, and a vector of covariates, respectively. standardize\_coxph fits a Cox proportional hazards model and the Breslow estimator of the baseline hazard in order to estimate the standardized survival function  $\theta(t,x) = E\{S(t|X = x, Z)\}\$  when measure = "survival" or the standardized restricted mean survival up to time t  $\theta(t,x) = E\{\int_0^t S(u|X=x)\}$  $x, Z/du$  when measure = "rmean", where t is a specific value of T, x is a specific value of X, and the expectation is over the marginal distribution of  $Z$ .

# Usage

```
standardize_coxph(
  formula,
  data,
  values,
  times,
 measure = c("survival", "rmean"),
 clusterid,
  ci\_level = 0.95,
  ci_type = "plain",contrasts = NULL,
  family = "gaussian",
  reference = NULL,
  transforms = NULL
\mathcal{L}
```
# Arguments



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#### Details

standardize\_coxph fits the Cox proportional hazards model

$$
\lambda(t|X,Z) = \lambda_0(t) \exp\{h(X,Z;\beta)\}.
$$

Breslow's estimator of the cumulative baseline hazard  $\Lambda_0(t) = \int_0^t \lambda_0(u) du$  is used together with the partial likelihood estimate of  $\beta$  to obtain estimates of the survival function  $S(t|X = x, Z)$  if measure = "survival":

$$
\hat{S}(t|X=x,Z) = \exp[-\hat{\Lambda}_0(t)\exp\{h(X=x,Z;\hat{\beta})\}].
$$

For each t in the t argument and for each x in the x argument, these estimates are averaged across all subjects (i.e. all observed values of  $Z$ ) to produce estimates

$$
\hat{\theta}(t,x) = \sum_{i=1}^{n} \hat{S}(t|X=x, Z_i)/n,
$$

where  $Z_i$  is the value of Z for subject i,  $i = 1, ..., n$ . The variance for  $\hat{\theta}(t, x)$  is obtained by the sandwich formula.

If measure = "rmean", then  $\Lambda_0(t)=\int_0^t\lambda_0(u)du$  is used together with the partial likelihood estimate of  $\beta$  to obtain estimates of the restricted mean survival up to time t:  $\int_0^t S(u|X = x, Z) du$ for each element of times. The estimation and inference is done using the method described in Chen and Tsiatis 2001. Currently, we can only estimate the difference in RMST for a single binary exposure. Two separate Cox models are fit for each level of the exposure, which is expected to be coded as 0/1.

#### Value

An object of class std\_surv. This is basically a list with components estimates and covariance estimates in res Results for transformations, contrasts, references are stored in res\_contrasts. The output contains estimates for contrasts and confidence intervals for all combinations of transforms and reference levels. Obtain numeric results in a data frame with the [tidy](#page-0-0) function.

#### Note

Standardized survival functions are sometimes referred to as (direct) adjusted survival functions in the literature.

standardize\_coxph/standardize\_parfrailty does not currently handle time-varying exposures or covariates.

standardize\_coxph/standardize\_parfrailty internally loops over all values in the t argument. Therefore, the function will usually be considerably faster if length(t) is small.

The variance calculation performed by standardize\_coxph does not condition on the observed covariates  $\overline{Z} = (Z_1, ..., Z_n)$ . To see how this matters, note that

$$
var\{\hat{\theta}(t,x)\} = E[var\{\hat{\theta}(t,x)|\bar{Z}\}] + var[E\{\hat{\theta}(t,x)|\bar{Z}\}].
$$

The usual parameter  $\beta$  in a Cox proportional hazards model does not depend on  $\bar{Z}$ . Thus,  $E(\hat{\beta}|\bar{Z})$  is independent of  $\bar{Z}$  as well (since  $E(\hat{\beta}|\bar{Z}) = \beta$ ), so that the term  $var[E\{\hat{\beta}|\bar{Z}\}]$  in the corresponding variance decomposition for  $var(\hat{\beta})$  becomes equal to 0. However,  $\theta(t, x)$  depends on  $\overline{Z}$  through the average over the sample distribution for Z, and thus the term  $var[E\{\hat{\theta}(t,x)|\bar{Z}\}]$  is not 0, unless one conditions on  $\bar{Z}$ . The variance calculation by Gail and Byar (1986) ignores this term, and thus effectively conditions on  $\overline{Z}$ .

#### Author(s)

Arvid Sjölander, Adam Brand, Michael Sachs

#### References

Chang I.M., Gelman G., Pagano M. (1982). Corrected group prognostic curves and summary statistics. *Journal of Chronic Diseases* 35, 669-674.

Gail M.H. and Byar D.P. (1986). Variance calculations for direct adjusted survival curves, with applications to testing for no treatment effect. *Biometrical Journal* 28(5), 587-599.

Makuch R.W. (1982). Adjusted survival curve estimation using covariates. *Journal of Chronic Diseases* 35, 437-443.

Sjölander A. (2016). Regression standardization with the R-package stdReg. *European Journal of Epidemiology* 31(6), 563-574.

Sjölander A. (2018). Estimation of causal effect measures with the R-package stdReg. *European Journal of Epidemiology* 33(9), 847-858.

Chen, P. Y., Tsiatis, A. A. (2001). Causal inference on the difference of the restricted mean lifetime between two groups. *Biometrics*, 57(4), 1030-1038.

```
require(survival)
set.seed(7)
n <- 300
Z \leftarrow \text{norm}(n)Zbin \leq rbinom(n, 1, .3)X \leq -rnorm(n, mean = Z)T <- rexp(n, rate = exp(X + Z + X * Z)) # survival time
C <- rexp(n, rate = exp(X + Z + X * Z)) # censoring time
fact <- factor(sample(letters[1:3], n, replace = TRUE))
U \leftarrow pmin(T, C) # time at risk
D \le - as.numeric(T \le C) # event indicator
dd <- data.frame(Z, Zbin, X, U, D, fact)
```
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```
fit.std.surv <- standardize_coxph(
 formula = Surv(U, D) ~ X + Z + X \times Z,
 data = dd,values = list(X = seq(-1, 1, 0.5)),times = 1:5)
print(fit.std.surv)
plot(fit.std.surv)
tidy(fit.std.surv)
fit.std <- standardize_coxph(
 formula = Surv(U, D) ~ X + Zbin + X * Zbin + fact,
 data = dd,
 values = list(Zbin = 0:1),
 times = 1.5,
 measure = "rmean",
 contrast = "difference",
 reference = 0
)
print(fit.std)
tidy(fit.std)
```
standardize\_gee *Regression standardization in conditional generalized estimating equations*

#### **Description**

standardize\_gee performs regression standardization in linear and log-linear fixed effects models, at specified values of the exposure, over the sample covariate distribution. Let  $Y$ ,  $X$ , and  $Z$  be the outcome, the exposure, and a vector of covariates, respectively. It is assumed that data are clustered with a cluster indicator  $i$ . standardize\_gee uses fitted fixed effects model, with cluster-specific intercept  $a_i$  (see details), to estimate the standardized mean  $\theta(x) = E\{E(Y|i, X = x, Z)\}\,$ where  $x$  is a specific value of  $X$ , and the outer expectation is over the marginal distribution of  $(a_i, Z)$ .

#### Usage

```
standardize_gee(
  formula,
  link = "identity",
  data,
  values,
  clusterid,
  case_control = FALSE,
  ci level = 0.95,
  ci_type = "plain",contrasts = NULL,
```

```
family = "gaussian",
  reference = NULL,
  transforms = NULL
\mathcal{L}
```
# Arguments



# Details

standardize\_gee assumes that a fixed effects model

$$
\eta\{E(Y|i, X, Z)\} = a_i + h(X, Z; \beta)
$$

has been fitted. The link function  $\eta$  is assumed to be the identity link or the log link. The conditional generalized estimating equation (CGEE) estimate of  $\beta$  is used to obtain estimates of the clusterspecific means:

$$
\hat{a}_i = \sum_{j=1}^{n_i} r_{ij} / n_i,
$$

where

$$
r_{ij} = Y_{ij} - h(X_{ij}, Z_{ij}; \hat{\beta})
$$

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if  $\eta$  is the identity link, and

$$
r_{ij} = Y_{ij} \exp\{-h(X_{ij}, Z_{ij}; \hat{\beta})\}
$$

if  $\eta$  is the log link, and  $(X_{ij}, Z_{ij})$  is the value of  $(X, Z)$  for subject j in cluster  $i, j = 1, ..., n_i, i =$ 1, ..., n. The CGEE estimate of  $\beta$  and the estimate of  $a_i$  are used to estimate the mean  $E(Y|i, X =$  $x, Z$ :

$$
\hat{E}(Y|i, X = x, Z) = \eta^{-1} \{ \hat{a}_i + h(X = x, Z; \hat{\beta}) \}.
$$

For each  $x$  in the x argument, these estimates are averaged across all subjects (i.e. all observed values of  $Z$  and all estimated values of  $a_i$ ) to produce estimates

$$
\hat{\theta}(x) = \sum_{i=1}^{n} \sum_{j=1}^{n_i} \hat{E}(Y|i, X = x, Z_i)/N,
$$

where  $N = \sum_{i=1}^{n} n_i$ . The variance for  $\hat{\theta}(x)$  is obtained by the sandwich formula.

#### Value

An object of class std\_glm. This is basically a list with components estimates and covariance estimates in res. Results for transformations, contrasts, references are stored in res\_contrasts. Obtain numeric results in a data frame with the [tidy](#page-0-0) function.

#### Note

The variance calculation performed by standardize\_gee does not condition on the observed covariates  $\bar{Z} = (Z_{11}, ..., Z_{nn_i})$ . To see how this matters, note that

$$
var\{\hat{\theta}(x)\} = E[var\{\hat{\theta}(x)|\bar{Z}\}] + var[E\{\hat{\theta}(x)|\bar{Z}\}].
$$

The usual parameter  $\beta$  in a generalized linear model does not depend on  $\bar{Z}$ . Thus,  $E(\hat{\beta}|\bar{Z})$  is independent of  $\bar{Z}$  as well (since  $E(\hat{\beta}|\bar{Z}) = \beta$ ), so that the term  $var[E\{\hat{\beta}|\bar{Z}\}]$  in the corresponding variance decomposition for  $var(\hat{\beta})$  becomes equal to 0. However,  $\theta(x)$  depends on  $\overline{Z}$  through the average over the sample distribution for Z, and thus the term  $var[E\{\hat{\theta}(x)|\bar{Z}\}]$  is not 0, unless one conditions on  $\bar{Z}$ .

#### Author(s)

Arvid Sjölander.

#### References

Goetgeluk S. and Vansteelandt S. (2008). Conditional generalized estimating equations for the analysis of clustered and longitudinal data. *Biometrics* 64(3), 772-780.

Martin R.S. (2017). Estimation of average marginal effects in multiplicative unobserved effects panel models. *Economics Letters* 160, 16-19.

Sjölander A. (2019). Estimation of marginal causal effects in the presence of confounding by cluster. *Biostatistics* doi: 10.1093/biostatistics/kxz054

#### Examples

```
require(drgee)
```

```
set.seed(4)
n < -300ni <- 2
id \leftarrow rep(1:n, each = ni)ai <- rep(rnorm(n), each = ni)
Z \le rnorm(n * ni)
X \leq -rnorm(n * ni, mean = ai + Z)Y \le - rnorm(n * ni, mean = ai + X + Z + 0.1 * X^2)
dd <- data.frame(id, Z, X, Y)
fit.std <- standardize_gee(
  formula = Y \sim X + Z + I(X^2),
 link = "identity",
  data = dd,values = list(X = seq(-3, 3, 0.5)),clusterid = "id"
\lambdaprint(fit.std)
plot(fit.std)
```
standardize\_glm *Get regression standardized estimates from a glm*

### Description

Get regression standardized estimates from a glm

# Usage

```
standardize_glm(
  formula,
 data,
  values,
  clusterid,
 matched_density_cases,
 matched_density_controls,
 matching_variable,
 p_population,
  case_control = FALSE,
 ci<sup>= 0.95</sup>,
  ci_type = "plain",contrasts = NULL,
  family = "gaussian",
  reference = NULL,
  transforms = NULL
)
```
<span id="page-17-0"></span>

#### <span id="page-18-0"></span>Arguments



# Details

standardize\_glm performs regression standardization in generalized linear models, at specified values of the exposure, over the sample covariate distribution. Let  $Y$ ,  $X$ , and  $Z$  be the outcome, the exposure, and a vector of covariates, respectively. standardize\_glm uses a fitted generalized linear model to estimate the standardized mean  $\theta(x) = E\{E(Y|X=x, Z)\}\)$ , where x is a specific value of  $X$ , and the outer expectation is over the marginal distribution of  $Z$ .

### Value

An object of class std\_glm. This is basically a list with components estimates and covariance estimates in res. Results for transformations, contrasts, references are stored in res\_contrasts. Obtain numeric results in a data frame with the [tidy](#page-0-0) function.

#### References

Rothman K.J., Greenland S., Lash T.L. (2008). *Modern Epidemiology*, 3rd edition. Lippincott, Williams & Wilkins.

Sjölander A. (2016). Regression standardization with the R-package stdReg. *European Journal of Epidemiology* 31(6), 563-574.

Sjölander A. (2016). Estimation of causal effect measures with the R-package stdReg. *European Journal of Epidemiology* 33(9), 847-858.

```
# basic example
# needs to correctly specify the outcome model and no unmeasered confounders
# (+ standard causal assunmptions)
set.seed(6)
n < -100Z \leftarrow \text{norm}(n)X \leq -rnorm(n, mean = Z)Y \le - rbinom(n, 1, prob = (1 + \exp(X + Z))^(-1))
dd \leftarrow data . frame(Z, X, Y)x <- standardize_glm(
  formula = Y \sim X * Z,
  family = "binomial",
  data = dd,values = list(X = 0:1),
  contrasts = c("difference", "ratio"),
  reference = 0\lambdax
# different transformations of causal effects
# example from Sjölander (2016) with case-control data
# here the matching variable needs to be passed as an argument
singapore <- AF::singapore
Mi <- singapore$Age
m < - mean(Mi)
s \leftarrow sd(Mi)d \leq -5standardize_glm(
  formula = Oesophagealcancer \sim (Everhotbev + Age + Dial + Samsu + Cigs)^22,
  family = binomial, data = singapore,
  values = list(Everhotbev = 0:1), clusterid = "Set",
  case_control = TRUE,
  matched\_density\_cases = function(x) \text{ donorm}(x, m, s),matched_density_controls = function(x) dnorm(x, m - d, s),
  matching_variable = Mi,
  p_population = 19.3 / 100000
)
# multiple exposures
set.seed(7)
n < - 100
```

```
Z \leftarrow \text{norm}(n)X1 \leq - \text{norm}(n, \text{mean} = Z)X2 \leq -rnorm(n)Y \le - rbinom(n, 1, prob = (1 + \exp(X1 + X2 + Z))^(-1))
dd <- data.frame(Z, X1, X2, Y)
x <- standardize_glm(
  formula = Y ~ X1 + X2 + Z,
  family = "binomial",
  data = dd, values = list(X1 = 0:1, X2 = 0:1),
  contrasts = c("difference", "ratio"),
  reference = c(X1 = 0, X2 = 0)\mathcal{L}x
tidy(x)
# continuous exposure
set.seed(2)
n <- 100
Z \leftarrow \text{norm}(n)X \leq -rnorm(n, mean = Z)Y \le - rnorm(n, mean = X + Z + 0.1 \times X^2)
dd <- data.frame(Z, X, Y)
x <- standardize_glm(
  formula = Y \sim X * Z,
  family = "gaussian",
  data = dd,values = list(X = seq(-1, 1, 0.1)))
# plot standardized mean as a function of x
plot(x)
# plot standardized mean - standardized mean at x = 0 as a function of x
plot(x, contrast = "difference", reference = 0)
```
standardize\_glm\_dr *Get regression standardized doubly-robust estimates from a glm*

# Description

Get regression standardized doubly-robust estimates from a glm

# Usage

```
standardize_glm_dr(
  formula_outcome,
  formula_exposure,
 data,
  values,
  ci level = 0.95,
```

```
ci_type = "plain",
 contrasts = NULL,
  family_outcome = "gaussian",
  family_exposure = "binomial",
  reference = NULL,
  transforms = NULL
)
```
#### Arguments



### Details

standardize\_glm\_dr performs regression standardization in generalized linear models, see e.g., documentation for standardize\_glm\_dr. Specifically, this version uses a doubly robust estimator for standardization, meaning inference is valid when either the outcome regression or the exposure model is correctly specified and there is no unmeasured confounding.

#### <span id="page-22-0"></span>Value

An object of class std\_glm. This is basically a list with components estimates and covariance estimates in res. Results for transformations, contrasts, references are stored in res\_contrasts. Obtain numeric results in a data frame with the [tidy](#page-0-0) function.

#### References

Gabriel E.E., Sachs, M.C., Martinussen T., Waernbaum I., Goetghebeur E., Vansteelandt S., Sjölander A. (2024), Inverse probability of treatment weighting with generalized linear outcome models for doubly robust estimation. *Statistics in Medicine*, 43(3):534–547.

#### Examples

```
# doubly robust estimator
# needs to correctly specify either the outcome model or the exposure model
# for confounding
# NOTE: only works with binary exposures
data <- AF::clslowbwt
x <- standardize_glm_dr(
  formula_outcome = bwt ~ smoker * (race + age + lwt) + I(age^2) + I(lwt^2),
  formula_exposure = smoker \sim race \star age \star lwt + I(age^2) + I(lwt^2),
  family_outcome = "gaussian"
  family_exposure = "binomial",
  data = data,
  values = list(smoker = c(\emptyset, 1)), contrasts = "difference", reference = \emptyset)
set.seed(6)
n < -100Z \leftarrow \text{norm}(n)X \le - rbinom(n, 1, prob = (1 + \exp(Z))^(-1))
Y \le - rbinom(n, 1, prob = (1 + \exp(X + Z))^(-1))
dd <- data.frame(Z, X, Y)
x <- standardize_glm_dr(
  formula_outcome = Y \sim X \times Z, formula_exposure = X \sim Z,
  family_outcome = "binomial",
  data = dd,
  values = list(X = 0:1), reference = 0,
  contrasts = c("difference"), transforms = c("odds"))
```
standardize\_level *Get standardized estimates using the g-formula with and separate models for each exposure level in the data*

#### **Description**

Get standardized estimates using the g-formula with and separate models for each exposure level in the data

# Usage

```
standardize_level(
 fitter_list,
 arguments,
 predict_fun_list,
 data,
 values,
 B = NULL,ci\_level = 0.95,
 contrasts = NULL,
 reference = NULL,
 seed = NULL,
 times = NULL,
 transforms = NULL,
 progressbar = TRUE
)
```
# Arguments



#### Details

See standardize. The difference is here that different models can be fitted for each value of x in values.

# Value

An object of class std\_custom. This is a list with components estimates and fit for the outcome model.

# References

Rothman K.J., Greenland S., Lash T.L. (2008). *Modern Epidemiology*, 3rd edition. Lippincott, Williams & Wilkins.

Sjölander A. (2016). Regression standardization with the R-package stdReg. *European Journal of Epidemiology* 31(6), 563-574.

Sjölander A. (2016). Estimation of causal effect measures with the R-package stdReg. *European Journal of Epidemiology* 33(9), 847-858.

```
require(survival)
prob_predict.coxph <- function(object, newdata, times) {
  fit.detail <- suppressWarnings(basehaz(object))
 cum.haz <- fit.detail$hazard[sapply(times, function(x) max(which(fit.detail$time <= x)))]
  predX <- predict(object = object, newdata = newdata, type = "risk")
  res \leq matrix(NA, ncol = length(times), nrow = length(predX))
  for (ti in seq_len(length(times))) {
    res[, ti] <- exp(-predX * cum.haz[ti])
  }
  res
}
set.seed(68)
n < -500Z \leftarrow \text{norm}(n)X \leq - rbinom(n, 1, prob = 0.5)
T <- rexp(n, rate = exp(X + Z + X * Z)) # survival time
C \leq rexp(n, rate = exp(X + Z + X \star Z)) # censoring time
U \le - pmin(T, C) # time at risk
D \le - as.numeric(T < C) # event indicator
dd <- data.frame(Z, X, U, D)
x <- standardize_level(
  fitter_list = list("coxph", "coxph"),
  arguments = list(
    list(
      formula = Surv(U, D) ~ X + Z + X * Z,
      method = "breslow",
     x = TRUE,
      y = TRUE),
```

```
list(
      formula = Surv(U, D) ~ X,
     method = "breslow",
     x = TRUE,y = TRUE)
 ),
 predict_fun_list = list(prob_predict.coxph, prob_predict.coxph),
 data = dd,
 times = seq(1, 5, 0.1),values = list(X = c(0, 1)),B = 100,reference = 0,
 contrasts = "difference"
\mathcal{L}print(x)
```
standardize\_parfrailty

```
Regression standardization in shared frailty gamma-Weibull models
```
### Description

standardize\_parfrailty performs regression standardization in shared frailty gamma-Weibull models, at specified values of the exposure, over the sample covariate distribution. Let  $T$ ,  $X$ , and  $Z$ be the survival outcome, the exposure, and a vector of covariates, respectively. standardize\_parfrailty fits a parametric frailty model to estimate the standardized survival function  $\theta(t, x) = E\{S(t|X =$  $x, Z$ }, where t is a specific value of T, x is a specific value of X, and the expectation is over the marginal distribution of Z.

# Usage

```
standardize_parfrailty(
  formula,
  data,
  values,
  times,
  clusterid,
  ci\_level = 0.95,
  ci_type = "plain",contrasts = NULL,
  family = "gaussian",
  reference = NULL,
  transforms = NULL
)
```
<span id="page-25-0"></span>

#### <span id="page-26-0"></span>Arguments



#### Details

standardize\_parfrailty fits a shared frailty gamma-Weibull model

$$
\lambda(t_{ij}|X_{ij}, Z_{ij}) = \lambda(t_{ij}; \alpha, \eta) U_i exp\{h(X_{ij}, Z_{ij}; \beta)\}
$$

, with parameterization as described in the help section for [parfrailty.](#page-2-1) Integrating out the gamma frailty gives the survival function

$$
S(t|X, Z) = [1 + \phi \Lambda_0(t; \alpha, \eta) \exp\{h(X, Z; \beta)\}]^{-1/\phi},
$$

where  $\Lambda_0(t; \alpha, \eta)$  is the cumulative baseline hazard

 $(t/\alpha)^{\eta}$ .

The ML estimates of  $(\alpha, \eta, \phi, \beta)$  are used to obtain estimates of the survival function  $S(t|X =$  $x, Z$ :

 $\hat{S}(t|X=x,Z)=[1+\hat{\phi}\Lambda_{0}(t;\hat{\alpha},\hat{\eta})\exp\{h(X,Z;\hat{\beta})\}]^{-1/\hat{\phi}}.$ 

<span id="page-27-0"></span>For each t in the t argument and for each  $x$  in the x argument, these estimates are averaged across all subjects (i.e. all observed values of  $Z$ ) to produce estimates

$$
\hat{\theta}(t,x) = \sum_{i=1}^{n} \hat{S}(t|X=x, Z_i)/n.
$$

The variance for  $\hat{\theta}(t, x)$  is obtained by the sandwich formula.

#### Value

An object of class std\_surv. This is basically a list with components estimates and covariance estimates in res Results for transformations, contrasts, references are stored in res\_contrasts. The output contains estimates for contrasts and confidence intervals for all combinations of transforms and reference levels. Obtain numeric results in a data frame with the [tidy](#page-0-0) function.

#### Note

Standardized survival functions are sometimes referred to as (direct) adjusted survival functions in the literature.

standardize\_coxph/standardize\_parfrailty does not currently handle time-varying exposures or covariates.

standardize\_coxph/standardize\_parfrailty internally loops over all values in the t argument. Therefore, the function will usually be considerably faster if length(t) is small.

The variance calculation performed by standardize\_coxph does not condition on the observed covariates  $\bar{Z} = (Z_1, ..., Z_n)$ . To see how this matters, note that

$$
var\{\hat{\theta}(t,x)\} = E[var\{\hat{\theta}(t,x)|\bar{Z}\}] + var[E\{\hat{\theta}(t,x)|\bar{Z}\}].
$$

The usual parameter  $\beta$  in a Cox proportional hazards model does not depend on  $\bar{Z}$ . Thus,  $E(\hat{\beta}|\bar{Z})$  is independent of  $\bar{Z}$  as well (since  $E(\hat{\beta}|\bar{Z}) = \beta$ ), so that the term  $var[E\{\hat{\beta}|\bar{Z}\}]$  in the corresponding variance decomposition for  $var(\hat{\beta})$  becomes equal to 0. However,  $\theta(t, x)$  depends on  $\overline{Z}$  through the average over the sample distribution for Z, and thus the term  $var[E\{\hat{\theta}(t,x)|\bar{Z}\}]$  is not 0, unless one conditions on  $\overline{Z}$ . The variance calculation by Gail and Byar (1986) ignores this term, and thus effectively conditions on  $\overline{Z}$ .

#### Author(s)

Arvid Sjölander

#### References

Chang I.M., Gelman G., Pagano M. (1982). Corrected group prognostic curves and summary statistics. *Journal of Chronic Diseases* 35, 669-674.

Dahlqwist E., Pawitan Y., Sjölander A. (2019). Regression standardization and attributable fraction estimation with between-within frailty models for clustered survival data. *Statistical Methods in Medical Research* 28(2), 462-485.

Gail M.H. and Byar D.P. (1986). Variance calculations for direct adjusted survival curves, with applications to testing for no treatment effect. *Biometrical Journal* 28(5), 587-599.

# <span id="page-28-0"></span>summary.parfrailty 29

Makuch R.W. (1982). Adjusted survival curve estimation using covariates. *Journal of Chronic Diseases* 35, 437-443.

```
require(survival)
# simulate data
set.seed(6)
n <- 300
m \leq -3alpha <-1.5eta <- 1
phi <- 0.5
beta <-1id \leftarrow rep(1:n, each = m)U \leftarrow \text{rep}(\text{rgamma}(n, \text{ shape} = 1 / \text{phi}, \text{scale} = \text{phi}), \text{each} = \text{m})X \leq -rnorm(n * m)# reparameterize scale as in rweibull function
weibull.scale <- alpha / (U * exp(beta * X))^(1 / eta)T <- rweibull(n \times m, shape = eta, scale = weibull.scale)
# right censoring
C <- runif(n * m, 0, 10)
D \le - as.numeric(T \le C)
T \leftarrow pmin(T, C)# strong left-truncation
L \le runif(n * m, 0, 2)
incl \leq T > L
incl \leq -</math> ave(x = incl, id, FUN = sum) == mdd <- data.frame(L, T, D, X, id)
dd <- dd[incl, ]
fit.std <- standardize_parfrailty(
  formula = Surv(L, T, D) \sim X,
  data = dd,values = list(X = seq(-1, 1, 0.5)),times = 1:5,
  clusterid = "id"
)
print(fit.std)
plot(fit.std)
```
This is a summary method for class "parfrailty".

# Usage

```
## S3 method for class 'parfrailty'
summary(
  object,
  ci_type = "plain",
  ci<sup>= 0.95</sup>,
  digits = max(3L, getOption("digits") - 3L),
  ...
\mathcal{L}
```
# Arguments



#### Value

An object of class "summary.parfrailty", which is a list that contains relevant summary statistics about the fitted model

# Author(s)

Arvid Sjölander and Elisabeth Dahlqwist.

# See Also

# [parfrailty](#page-2-1)

# Examples

## See documentation for parfrailty

<span id="page-29-0"></span>

<span id="page-30-0"></span>

Tidy summarizes information about the components of the standardized regression fit.

#### Usage

## S3 method for class 'std\_glm' tidy(x, ...)

# Arguments



#### Value

A data.frame

```
set.seed(6)
n <- 100
Z \leftarrow \text{norm}(n)X \leq -rnorm(n, mean = Z)Y \le - rbinom(n, 1, prob = (1 + \exp(X + Z))^(-1))
dd <- data.frame(Z, X, Y)
x <- standardize_glm(
  formula = Y \sim X * Z,
  family = "binomial",
  data = dd,values = list(X = 0:1),
  contrasts = c("difference", "ratio"),
  reference = 0
\overline{\phantom{a}}tidy(x)
```
<span id="page-31-0"></span>

Tidy summarizes information about the components of the standardized model fit.

#### Usage

## S3 method for class 'std\_surv' tidy $(x, \ldots)$ 

# Arguments



# Value

A data.frame

```
require(survival)
set.seed(8)
n < -300Z \leftarrow \text{norm}(n)X \leq -rnorm(n, mean = Z)time \leq rexp(n, rate = exp(X + Z + X * Z)) # survival time
C <- r \exp(n, r \text{ate} = \exp(X + Z + X * Z)) # censoring time
U <- pmin(time, C) # time at risk
D \le - as.numeric(time \le C) # event indicator
dd <- data.frame(Z, X, U, D)
x <- standardize_coxph(
  formula = Surv(U, D) ~ X + Z + X * Z,
  data = dd, values = list(X = seq(-1, 1, 0.5)), times = c(2,3,4)\mathcal{L}
```

```
tidy(x)
```
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