

Package ‘iCARE’

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Title A Tool for Individualized Coherent Absolute Risk Estimation
(iCARE)

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Description An R package to compute Individualized Coherent Absolute Risk Estimators.

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bc_data

*Data for examples***Description**

Example data for `computeAbsoluteRisk`, `computeAbsoluteRiskSplitInterval`, `ModelValidation`, and `plotModelValidation`.

Details

- `bc_model_cov_info`: a main list containing information on family history and parity; information on each risk factor is given as a list
- `bc_15_snps`: contains published SNP information from reference (2)
- `bc_model_log_or`: vector of log-odds ratios of family history and parity
- `bc_model_log_or_post_50`: vector of log-odds ratios of family history and parity for women 50 years or older
- `ref_cov_dat`: contains a subsample of data imputed using reference (4) and (5)
- `ref_cov_dat_post_50`: contains a subsample of the data on family history and parity, to be used as reference dataset for women 50 years or older
- `bc_inc`: contains age-specific incidence rates of breast cancer from reference (3)
- `mort_inc`: contains age-specific incidence rates of all-cause mortality from reference (1) below
- `new_cov_prof`: Information on family history and parity for three women (given for illustration of absolute risk prediction)
- `new_snp_prof`: Information on 15 breast cancer associated SNPs for three women (given for illustration of absolute risk prediction)
- `validation.cohort.data`: Simulated full cohort dataset of 50,000 women for illustration of model validation. The variables are:
 - `id`: Subject id
 - `famhist`: Family history; binary indicator of presence/absence of first degree relatives
 - `parity`: Number of child births
 - `study.entry.age`: age of study entry
 - `study.exit.age`: age of study exit
 - `observed.outcome`: binary indicator of disease status (yes/no)
 - `time.of.onset`: time (in years) since study entry to the development of disease; for subjects who have not developed disease beyond the observed followup, it is set to `Inf`
 - `observed.followup`: number of years the subject is followed up in the study (difference between the age of study exit and age of study entry)
- `validation.nested.case.control.data`: A simulated example of a case-control study of 2694 women, nested within the full cohort. In addition to the variables given above, it has information on the 15 breast cancer associated SNPs with variable names being the rs-identifiers.

References

- (1) Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Underlying Cause of Death 1999-2011 on CDC WONDER Online Database, released 2014. Data are from the Multiple Cause of Death Files, 1999-2011, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at <http://wonder.cdc.gov/ucd-icd10.html> on Aug 26, 2014.
- (2) Michailidou K, Beesley J, Lindstrom S, et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nature genetics* 2015;47:373-80.
- (3) Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2011 Sub, Vintage 2009 Pops (2000-2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2010 Counties. In: National Cancer Institute D, Surveillance Research Program, Surveillance Systems Branch, ed. SEER18 ed.
- (4) 2010 National Health Interview Survey (NHIS) Public Use Data Release, NHIS Survey Description. 2011. (Accessed at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHIS/2010/srvydesc.pdf.)
- (5) Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2010.

Examples

```
temp <- data(bc_data, package="iCARE")

# Display the object names
temp
```

computeAbsoluteRisk *Building and Applying an Absolute Risk Model*

Description

This function is used to build absolute risk models and apply them to estimate absolute risks.

Usage

```
computeAbsoluteRisk(model.formula = NULL, model.cov.info = NULL,
  model.snp.info = NULL, model.log.RR = NULL, model.ref.dataset = NULL,
  model.ref.dataset.weights = NULL, model.disease.incidence.rates,
  model.competing.incidence.rates = NULL, model.bin.fh.name = NA,
  n.imp = 5, apply.age.start, apply.age.interval.length,
  apply.cov.profile = NULL, apply.snp.profile = NULL, use.c.code = 1,
  return.lp = FALSE, return.refs.risk = FALSE)
```

Arguments

- `model.formula` an object of class `formula`: a symbolic description of the model to be fitted, e.g. `Y~Parity+FamilyHistory`.
- `model.cov.info` contains information about the risk factors in the model ; a main list containing a list for each covariate, which must have the fields:
- `"name"` : a string with the covariate name, matching name in `model.formula`
 - `"type"` : a string that is either `"continuous"` or `"factor"`.
- If factor variable, then:
- `"levels"` : vector with strings of level names
 - `"ref"` : optional field, string with name of referent level
- `model.snp.info` dataframe with three columns, named: [`"snp.name"`, `"snp.odds.ratio"`, `"snp.freq"`]
- `model.log.RR` vector with log odds ratios corresponding to the model params; no intercept; names must match design matrix arising from `model.formula` and `model.cov.info`; check names using function `check_design_matrix()`.
- `model.ref.dataset` dataframe of risk factors for a sample of subjects representative of underlying population, no missing values. Variables must be in same order with same names as in `model.formula`.
- `model.ref.dataset.weights` optional vector of sampling weights for `model.ref.dataset`.
- `model.disease.incidence.rates` two column matrix [integer ages, incidence rates] or three column matrix [start age, end age, rate] with incidence rate of disease. Must fully cover age interval for estimation.
- `model.competing.incidence.rates` two column matrix [integer ages, incidence rates] or three column matrix [start age, end age, rate] with incidence rate of competing events. Must fully cover age interval for estimation.
- `model.bin.fh.name` string name of family history variable, if in model. This must refer to a variable that only takes values 0,1, NA.
- `n.imp` integer value for number of imputations for handling missing SNPs.
- `apply.age.start` single integer or vector of integer ages for the start of the interval over which to compute absolute risk.
- `apply.age.interval.length` single integer or vector of integer years over which absolute risk should be computed.
- `apply.cov.profile` dataframe containing the covariate profiles for which absolute risk will be computed. Covariates must be in same order with same names as in `model.formula`.
- `apply.snp.profile` data frame with observed SNP data (coded 0,1, 2, or NA). May have missing values.


```

                                apply.snp.profile = new_snp_prof,
                                return.refs.risk  = TRUE)
summary(results)
plot(results, main="Risk")
boxplot(results$risk ~ new_cov_prof$famhist, na.rm=TRUE)

```

```
computeAbsoluteRiskSplitInterval
```

Building and Applying an Absolute Risk Model: Compute Risk over Interval Split in Two Parts

Description

This function is used to build an absolute risk model that incorporates different input parameters before and after a given time point. The model is then applied to estimate absolute risks.

Usage

```

computeAbsoluteRiskSplitInterval(apply.age.start, apply.age.interval.length,
  apply.cov.profile, model.formula, model.disease.incidence.rates,
  model.log.RR, model.ref.dataset, model.ref.dataset.weights=NULL,
  model.cov.info, use.c.code=1, model.competing.incidence.rates=NULL,
  return.lp=FALSE, apply.snp.profile=NULL, model.snp.info=NULL,
  model.bin.fh.name=NULL, cut.time=NULL, apply.cov.profile.2=NULL,
  model.formula.2=NULL, model.log.RR.2=NULL, model.ref.dataset.2=NULL,
  model.ref.dataset.weights.2=NULL, model.cov.info.2=NULL,
  model.bin.fh.name.2=NULL, n.imp=5, return.refs.risk=FALSE)

```

Arguments

`apply.age.start` single integer or vector of integer ages for the start of the interval over which to compute absolute risk.

`apply.age.interval.length` single integer or vector of integer years over which absolute risk should be computed.

`apply.cov.profile` dataframe containing the covariate profiles for which absolute risk will be computed. Covariates must be in same order with same names as in `model.formula`.

`model.formula` an object of class `formula`: a symbolic description of the model to be fitted, e.g. `Y~Parity+FamilyHistory`.

`model.disease.incidence.rates` two column matrix [integer ages, incidence rates] or three column matrix [start age, end age, rate] with incidence rate of disease. Must fully cover age interval for estimation.

`model.log.RR` vector with log odds ratios corresponding to the model params; no intercept; names must match design matrix arising from `model.formula` and `model.cov.info`; check names using function `check_design_matrix()`.

model.ref.dataset	dataframe of risk factors for a sample of subjects representative of underlying population, no missing values. Variables must be in same order with same names as in model.formula.
model.ref.dataset.weights	optional vector of sampling weights for model.ref.dataset.
model.cov.info	contains information about the risk factors in the model ; a main list containing a list for each covariate, which must have the fields: <ul style="list-style-type: none"> • "name" : a string with the covariate name, matching name in model.formula • "type" : a string that is either "continuous" or "factor". If factor variable, then: <ul style="list-style-type: none"> • "levels" : vector with strings of level names • "ref" : optional field, string with name of referent level
use.c.code	binary indicator of whether to run the c program for fast computation.
model.competing.incidence.rates	two column matrix [integer ages, incidence rates] or three column matrix [start age, end age, rate] with incidence rate of competing events. Must fully cover age interval for estimation.
return.lp	binary indicator of whether to return the linear predictor for each subject in apply.cov.profile.
apply.snp.profile	data frame with observed SNP data (coded 0,1, 2, or NA). May have missing values.
model.snp.info	dataframe with three columns [rs number, odds ratio, allele frequency]
model.bin.fh.name	string name of family history variable, if in model. This must refer to a variable that only takes values 0,1, NA.
cut.time	integer age for which to split computation into before and after
apply.cov.profile.2	see apply.cov.profile, to be used for estimation in ages after the cutpoint
model.formula.2	see model.formula, to be used for estimation in ages after the cutpoint
model.log.RR.2	see model.log.RR, to be used for estimation in ages after the cutpoint
model.ref.dataset.2	see model.ref.dataset, to be used for estimation in ages after the cutpoint
model.ref.dataset.weights.2	see model.ref.dataset.weights, to be used for estimation in ages after the cutpoint
model.cov.info.2	see model.cov.info, to be used for estimation in ages after the cutpoint
model.bin.fh.name.2	see model.bin.fh.name, to be used for estimation in ages after the cutpoint
n.imp	integer value for number of imputations for handling missing SNPs.
return.refs.risk	binary indicator of whether to return the absolute risk prediction for each subject in model.ref.dataset.


```
apply.cov.profile = new_cov_prof,  
apply.snp.profile = new_snp_prof,  
return.refs.risk = TRUE)  
  
summary(results)  
plot(results)  
boxplot(results$risk ~ new_cov_prof$famhist, na.rm=TRUE)
```

Description

Individualized Coherent Absolute Risk Estimators (iCARE) is a tool that allows researchers to quickly build models for absolute risk and apply them to estimate individuals' risk based on a set of user defined input parameters. The software gives users the flexibility to change or update models rapidly based on new risk factors or tailor models to different populations based on the specification of simply three input arguments: (1) a model for relative risk assumed to be externally derived (2) an age-specific disease incidence rate and (3) the distribution of risk factors for the population of interest. The tool can handle missing information on risk factors for risk estimation using an approach where all estimates are derived from a single model through appropriate model averaging.

Details

The main functions for building and applying an absolute risk model are [computeAbsoluteRisk](#) and [computeAbsoluteRiskSplitInterval](#). The first of these computes absolute risks over the specified time interval using a single set of parameters. The second provides more advanced functionality and computes absolute risk over the interval in two parts.

[computeAbsoluteRiskSplitInterval](#) allows the user compute absolute risk over the interval in two parts, incorporating two different sets of parameters before and after a specified cutpoint. This function allows a different cutpoint for each covariate profile if desired. The function for validating an absolute risk model is [ModelValidation](#), and [plotModelValidation](#) can be called for producing plots for model calibration, model discrimination and incidence rates.

Author(s)

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Description

This function is used to validate absolute risk models.

Usage

```

ModelValidation(study.data,
               total.followup.validation = FALSE,
               predicted.risk = NULL,
               predicted.risk.interval = NULL,
               linear.predictor = NULL,
               iCARE.model.object =
                 list(model.formula = NULL,
                     model.cov.info = NULL,
                     model.snp.info = NULL,
                     model.log.RR = NULL,
                     model.ref.dataset = NULL,
                     model.ref.dataset.weights = NULL,
                     model.disease.incidence.rates = NULL,
                     model.competing.incidence.rates = NULL,
                     model.bin.fh.name = NA,
                     apply.cov.profile = NULL,
                     apply.snp.profile = NULL,
                     n.imp = 5, use.c.code = 1,
                     return.lp = TRUE,
                     return.refs.risk = TRUE),
               number.of.percentiles = 10,
               reference.entry.age = NULL,
               reference.exit.age = NULL,
               predicted.risk.ref = NULL,
               linear.predictor.ref = NULL,
               linear.predictor.cutoffs = NULL,
               dataset = "Example Dataset",
               model.name = "Example Risk Prediction Model")

```

Arguments

<code>study.data</code>	Data frame which includes the variables below. <ul style="list-style-type: none"> • <code>observed.outcome</code>: 1 if disease has occurred by the end of followup, 0 if censored • <code>study.entry.age</code>: age (in years) of entering the cohort • <code>study.exit.age</code>: age (in years) of last followup visit • <code>time.of.onset</code>: time (in years) of onset of disease; note that all subjects are disease free at the time of entry and for those who do not develop disease by end of followup it is Inf • <code>sampling.weights</code>: for a case-control study nested within a cohort study, this is a vector of sampling weights for each subject, i.e., probability of inclusion into the sample
<code>total.followup.validation</code>	logical; TRUE if risk validation is performed over the total followup, for all other cases (e.g., 5 year or 10 year risk validation) it is FALSE
<code>predicted.risk</code>	vector of predicted risks; should be supplied if risk prediction is done by some method other than that implemented in iCARE; default is NULL
<code>predicted.risk.interval</code>	scalar or vector denoting the number of years after entering the study over which risk validation is desired (e.g., 5 for validating a model for 5 year risk) if

	total.followup.validation = FALSE; if total.followup.validation = TRUE, it can be set to NULL
linear.predictor	vector of risk scores for each subject, i.e. $x \cdot \beta$, where x is the vector of risk factors and β is the vector of log relative risks; in the current version if both the arguments predicted.risk and linear.predictor are supplied the function will use the supplied estimates to perform model validation, otherwise the function will compute these estimates using the computeAbsoluteRisk function
iCARE.model.object	A named list containing the input arguments to the function computeAbsoluteRisk . The names in this list must match the argument names. See computeAbsoluteRisk
number.of.percentiles	the number of percentiles of the risk score that determines the number of strata over which the risk prediction model is to be validated, default = 10
reference.entry.age	age of entry to be specified for computing absolute risk of the reference population
reference.exit.age	age of exit to be specified for computing absolute risk of the reference population
predicted.risk.ref	predicted absolute risk in the reference population assuming the entry age to be as specified in reference.entry.age and exit age to be as specified in reference.exit.age
linear.predictor.ref	vector of risk scores for the reference population
linear.predictor.cutoffs	user specified cut-points for the linear predictor to define categories for absolute risk calibration and relative risk calibration
dataset	name and type of dataset to be displayed in the output, e.g., "PLCO Full Cohort" or "Full Cohort Simulation"
model.name	name of the model to be displayed in output, e.g., "Synthetic Model" or "Simulation Setting"

Value

This function returns a list of the following objects:

- Subject_Specific_Observed_Outcome: observed outcome after adjusting the observed followup according to the risk prediction interval: 1 if disease has occurred by the end of followup, 0 if censored
- Risk_Prediction_Interval: Character object showing the interval of risk prediction (e.g., 5 years). If the risk prediction is over the total followup of the study, this reads "Observed Followup"
- Adjusted.Followup: followup time (in years) after adjusting the observed followup according to the risk prediction interval
- Subject_Specific_Predicted_Absolute_Risk: predicted absolute risk of disease for each subject
- Reference_Absolute_Risk: predicted absolute risk in the reference population

- `Subject_Specific_Risk_Score`: estimated risk score for each subject; the missing covariates are handled internally using the imputation in iCARE
- `Reference_Risk_Score`: risk score for the reference population
- `Population_Incidence_Rate`: age specific disease incidence rate in the population
- `Study_Incidence_Rate`: estimated age specific incidence rate in the study
- `Category_Results`: observed and predicted absolute risks and observed and predicted relative risks in each category defined by the risk score
- `Category_Specific_Observed_Absolute_Risk`: Observed absolute risk in each category defined by the risk score
- `Category_Specific_Predicted_Absolute_Risk`: Predicted absolute risk in each category defined by the risk score
- `Category_Specific_Observed_Relative_Risk`: Observed relative risk in each category defined by the risk score
- `Category_Specific_Predicted_Relative_Risk`: Predicted relative risk in each category defined by the risk score
- `Variance_Matrix_Absolute_Risk`: Variance-covariance matrix of the vector of category specific absolute risks
- `Variance_Matrix_LogRelative_Risk`: Variance-covariance matrix of the vector of category specific relative risks
- `Hosmer_Lemeshow_Results`: results of the Hosmer-Lemeshow type chisquare test comparing the observed and predicted absolute risks
- `HL_pvalue`: pvalue of the Hosmer-Lemeshow type chisquare test
- `RR_test_result`: results of the chisquare test comparing the observed and predicted relative risks
- `RR_test_pvalue`: pvalue of the chisquare test of relative risk
- `AUC`: estimate of the Area Under the Curve (AUC) defined as the probability that for a randomly sampled case-control pair the case has a higher risk score than the control; for the full cohort setting we compute the empirical proportion and for the nested case-control setting we compute the inverse probability weighted estimator
- `Variance_AUC`: estimate of the variance of Area Under the Curve (AUC): for the full cohort setting the regular asymptotic variance is estimated and for the nested case-control setting the influence function based variance estimate of the inverse probability weighted variance estimator is computed
- `CI_AUC`: 95 percent Wald based confidence interval of Area Under the Curve (AUC) using the asymptotic variance
- `Overall_Expected_to_Observed_Ratio`: The overall ratio of the expected risk to the observed risk
- `CI_Overall_Expected_to_Observed_Ratio`: 95 percent Wald based confidence interval of the overall ratio of the expected risk to the observed risk

See Also

[computeAbsoluteRisk](#)

Examples

```

data(bc_data, package="iCARE")
validation.cohort.data$inclusion = 0
subjects_included = intersect(validation.cohort.data$id,
                              validation.nested.case.control.data$id)
validation.cohort.data$inclusion[subjects_included] = 1

validation.cohort.data$observed.followup = validation.cohort.data$study.exit.age -
  validation.cohort.data$study.entry.age

selection.model = glm(inclusion ~ observed.outcome
                      * (study.entry.age + observed.followup),
                      data = validation.cohort.data,
                      family = binomial(link = "logit"))

validation.nested.case.control.data$sampling.weights =
  selection.model$fitted.values[validation.cohort.data$inclusion == 1]

set.seed(50)

bc_model_formula = observed.outcome ~ famhist + as.factor(parity)
data = validation.nested.case.control.data

risk.model = list(model.formula = bc_model_formula,
                  model.cov.info = bc_model_cov_info,
                  model.snp.info = bc_15_snps,
                  model.log.RR = bc_model_log_or,
                  model.ref.dataset = ref_cov_dat,
                  model.ref.dataset.weights = NULL,
                  model.disease.incidence.rates = bc_inc,
                  model.competing.incidence.rates = mort_inc,
                  model.bin.fh.name = "famhist",
                  apply.cov.profile = data[,all.vars(bc_model_formula)[-1]],
                  apply.snp.profile = data[,bc_15_snps$snp.name],
                  n.imp = 5, use.c.code = 1, return.lp = TRUE,
                  return.refs.risk = TRUE)

ModelValidation(study.data = data,
                total.followup.validation = TRUE,
                predicted.risk.interval = NULL,
                iCARE.model.object = risk.model,
                number.of.percentiles = 10)

```

plotModelValidation *Model Validation Plot*

Description

This function is used to create plots for model calibration, model discrimination and incidence rates.

Usage

```
plotModelValidation(study.data, validation.results,
```

```

dataset = "Example Dataset",
model.name = "Example Model",
x.lim.absrisk = "",
y.lim.absrisk = "",
x.lab.absrisk = "Expected Absolute Risk (%)",
y.lab.absrisk = "Observed Absolute Risk (%)",
x.lim.RR = "",
y.lim.RR = "", x.lab.RR = "Expected Relative Risk",
y.lab.RR = "Observed Relative Risk",
risk.score.plot.kernel = "gaussian",
risk.score.plot.bandwidth = "nrd0",
risk.score.plot.percent.smooth = 50)

```

Arguments

study.data	See ModelValidation
validation.results	List returned from ModelValidation
dataset	Name and type of dataset to be displayed in the output, e.g., "PLCO Full Cohort" or "Full Cohort Simulation"
model.name	Name of the model to be displayed in output, e.g., "Synthetic Model" or "Simulation Setting"
x.lim.absrisk	Vector of length two specifying the x-axes limits in the absolute risk calibration plot. If not specified, then default limits will be computed.
y.lim.absrisk	Vector of length two specifying the y-axes limits in the absolute risk calibration plot. If not specified, then default limits will be computed.
x.lab.absrisk	String specifying the x-axes label in the absolute risk calibration plot. The default is "Expected Absolute Risk (%)".
y.lab.absrisk	String specifying the y-axes label in the absolute risk calibration plot. The default is "Observed Absolute Risk (%)".
x.lim.RR	Vector of length two specifying the x-axes limits in the relative risk calibration plot. If not specified, then default limits will be computed.
y.lim.RR	Vector of length two specifying the y-axes limits in the relative risk calibration plot. If not specified, then default limits will be computed.
x.lab.RR	String specifying the x-axes label in the relative risk calibration plot. The default is "Expected Relative Risk".
y.lab.RR	String specifying the y-axes label in the relative risk calibration plot. The default is "Observed Relative Risk".
risk.score.plot.kernel	Character string giving the smoothing kernel to be used by the density function used internally to plot the density of the risk scores. It should be one of "gaussian", "rectangular", "triangular", "epanechnikov", "biweight", "cosine" or "optcosine", with default "gaussian".
risk.score.plot.bandwidth	The options for bandwidth selection used by the density function internally to plot the density of the risk scores. The options are one of the following: "nrd0", "nrd", "ucv", "bcv", "SJ-ste", "SJ-dpi" with the default being "nrd0". More information on these different options is available in the help pages that can be accessed from R using the command <code>?bw.nrd</code> .


```
number.of.percentiles = 10)  
  
plot(output)
```

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