

iCARE (Individualized Coherent Absolute Risk Estimation) Package

October 26, 2021

Load the iCARE library

```
> library(iCARE)
```

Load the breast cancer data and set the seed.

```
> data("bc_data", package="iCARE")
> set.seed(50)
```

Example 1: SNP-only model

In this example, we will estimate the risk of breast cancer in ages 50-80. A SNP-only model is fit, with no specific genotypes supplied for estimation. The population disease rates are from SEER.

```
> res_snps_miss = computeAbsoluteRisk(model.snp.info = bc_72_snps,
+                                     model.disease.incidence.rates = bc_inc,
+                                     model.competing.incidence.rates = mort_inc,
+                                     apply.age.start = 50, apply.age.interval.length = 30,
+                                     return.refs.risk = TRUE)
```

Note: You did not provide apply.snp.profile. Will impute SNPs for 10000 people.
If require more, please provide apply.snp.profile input.

```
[1] "Note: As specified, the model does not adjust SNP imputations for family history."
      user system elapsed
      8.24    0.11    8.34
```

Compute a summary of the risks.

```
> summary(res_snps_miss$refs.risk)

      Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.05745 0.08666 0.09494 0.09600 0.10422 0.15882
```

Next, suppose we want to predict risk for three specific women whom we have genotyped; we can then call:

```

> res_snps_dat = computeAbsoluteRisk(model.snp.info = bc_72_snps,
+                                   model.disease.incidence.rates = bc_inc,
+                                   model.competing.incidence.rates = mort_inc,
+                                   apply.age.start = 50, apply.age.interval.length = 30,
+                                   apply.snp.profile = new_snp_prof,
+                                   return.refs.risk = TRUE)

[1] "Note: As specified, the model does not adjust SNP imputations for family history."
    user  system elapsed
 0.36    0.10    0.45

> names(res_snps_dat)

[1] "risk"      "details"   "beta.used" "refs.risk"

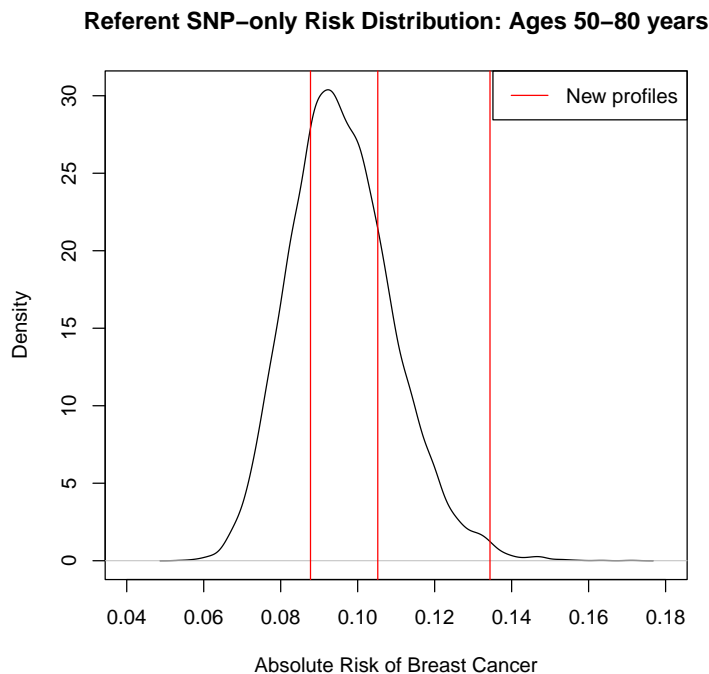
```

These results allow us to create a useful plot showing the distribution of risks in our reference dataset and to add the risks of the three women to see where they fall on the population distribution.

```

> plot(density(res_snps_dat$refs.risk),
+       xlim = c(0.04,0.18), xlab = "Absolute Risk of Breast Cancer",
+       main = "Referent SNP-only Risk Distribution: Ages 50-80 years")
> abline(v = res_snps_dat$risk, col = "red")
> legend("topright", legend = "New profiles", col = "red", lwd = 1)

```



Example 2: Breast cancer risk model with risk-factors and SNPs

In this example, we will estimate the risk of breast cancer in ages 50-80 by fitting a model with classical risk factors and 72 SNPs, with three specific covariate profiles supplied for estimation (with some missing data). More details on risk factors are available in the manual.

```
> res_covs_snps = computeAbsoluteRisk(model.formula = bc_model_formula,
+                                     model.cov.info = bc_model_cov_info,
+                                     model.snp.info = bc_72_snps,
+                                     model.log.RR = bc_model_log_or,
+                                     model.ref.dataset = ref_cov_dat,
+                                     model.disease.incidence.rates = bc_inc,
+                                     model.competing.incidence.rates = mort_inc,
+                                     model.bin.fh.name = "famhist",
+                                     apply.age.start = 50,
+                                     apply.age.interval.length = 30,
+                                     apply.cov.profile = new_cov_prof,
+                                     apply.snp.profile = new_snp_prof,
+                                     return.refs.risk = TRUE)

user  system elapsed
1.16   0.14   1.29
```

In addition to summarizing and plotting the risk estimates, iCARE includes an option to view more detailed output, by calling:

```
> print(res_covs_snps$details)
```

	Int_Start	Int_End	Risk_Estimate	rs616488	rs11552449	rs11249433	rs12405132
1	50	80	0.10240752	NA	NA	NA	NA
2	50	80	0.08994616	2	0	NA	NA
3	50	80	0.16910925	2	0	1	1
	rs12048493	rs6678914	rs4245739	rs72755295	rs12710696	rs4849887	rs2016394
1	NA	0	0	0	0	0	0
2	NA	NA	NA	NA	1	1	0
3	1	1	1	0	2	0	0
	rs1550623	rs16857609	rs6762644	rs4973768	rs12493607	rs6796502	rs9790517
1	0	0	0	1	1	0	1
2	0	2	1	1	1	1	2
3	0	0	0	2	1	0	1
	rs6828523	rs10069690	rs13162653	rs2012709	rs10941679	rs10472076	rs1353747
1	0	1	2	0	0	2	0
2	0	0	1	0	0	1	1
3	0	0	1	0	0	0	1
	rs7707921	rs1432679	rs11242675	rs204247	rs9257408	rs4593472	rs720475
1	0	1	2	0	0	1	1
2	0	0	1	2	1	1	0
3	1	2	1	2	1	1	0
	rs9693444	rs13365225	rs6472903	rs2943559	rs13267382	rs11780156	rs1011970

1	1	1	1	0	0	0	0
2	0	0	1	0	2	1	1
3	1	1	0	0	1	0	0
	rs10759243	rs2380205	rs7072776	rs11814448	rs7904519	rs11199914	rs554219
1	0	2	2	0	0	1	1
2	1	0	0	0	0	0	0
3	1	1	1	0	2	0	1
	rs75915166	rs11820646	rs12422552	rs17356907	rs1292011	rs11571833	rs2236007
1	0	1	1	0	1	0	1
2	0	0	0	0	0	0	0
3	0	1	1	0	2	0	0
	rs2588809	rs999737	rs941764	rs11627032	rs17817449	rs11075995	rs13329835
1	0	0	1	0	1	1	1
2	1	0	0	1	1	1	0
3	0	0	1	0	0	1	1
	rs146699004	rs745570	rs527616	rs1436904	rs6507583	rs4808801	rs3760982
1	0	0	0	0	0	1	0
2	1	2	0	0	0	1	1
3	1	2	1	1	0	1	1
	rs2284378	rs2823093	rs17879961	rs132390	rs6001930	famhist	menarche_dec
1	1	1	0	0	0	0	8
2	1	0	0	0	0	0	10
3	0	0	0	0	0	0	1
	birth_dec	agemeno_dec	height_dec	bmi_dec	rd_menohrt	rd2_everhrt_e	
1	2	2	6	10	1	0	
2	2	1	6	4	1	0	
3	1	7	1	10	1	0	
	rd2_everhrt_c	rd2_currhrt	alcoholweek_dec	ever_smoke			
1	0	0	1	1			
2	0	0	6	0			
3	0	0	1	1			

Illustration of the validation component

We want to validate a model for predicting absolute risk of disease based on a combined model of classical risk factors and 72 SNPs using the nested case-control dataset.

The first step is to compute sampling weights. We fit a logistic regression model of inclusion depending on the case/control status, age of study entry and observed followup using the R function **glm**, as shown below:

```
> 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]

```

The next step is to call the **ModelValidation** function to implement the validation analysis.

```

> 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_72_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_72_snps$snp.name],
+                   n.imp = 5, use.c.code = 1, return.lp = TRUE,
+                   return.refs.risk = TRUE)
> output = ModelValidation(study.data = data,
+                          total.followup.validation = TRUE,
+                          predicted.risk.interval = NULL,
+                          iCARE.model.object = risk.model,
+                          number.of.percentiles = 10)

```

```

user  system elapsed
94.67   0.09   94.76

```

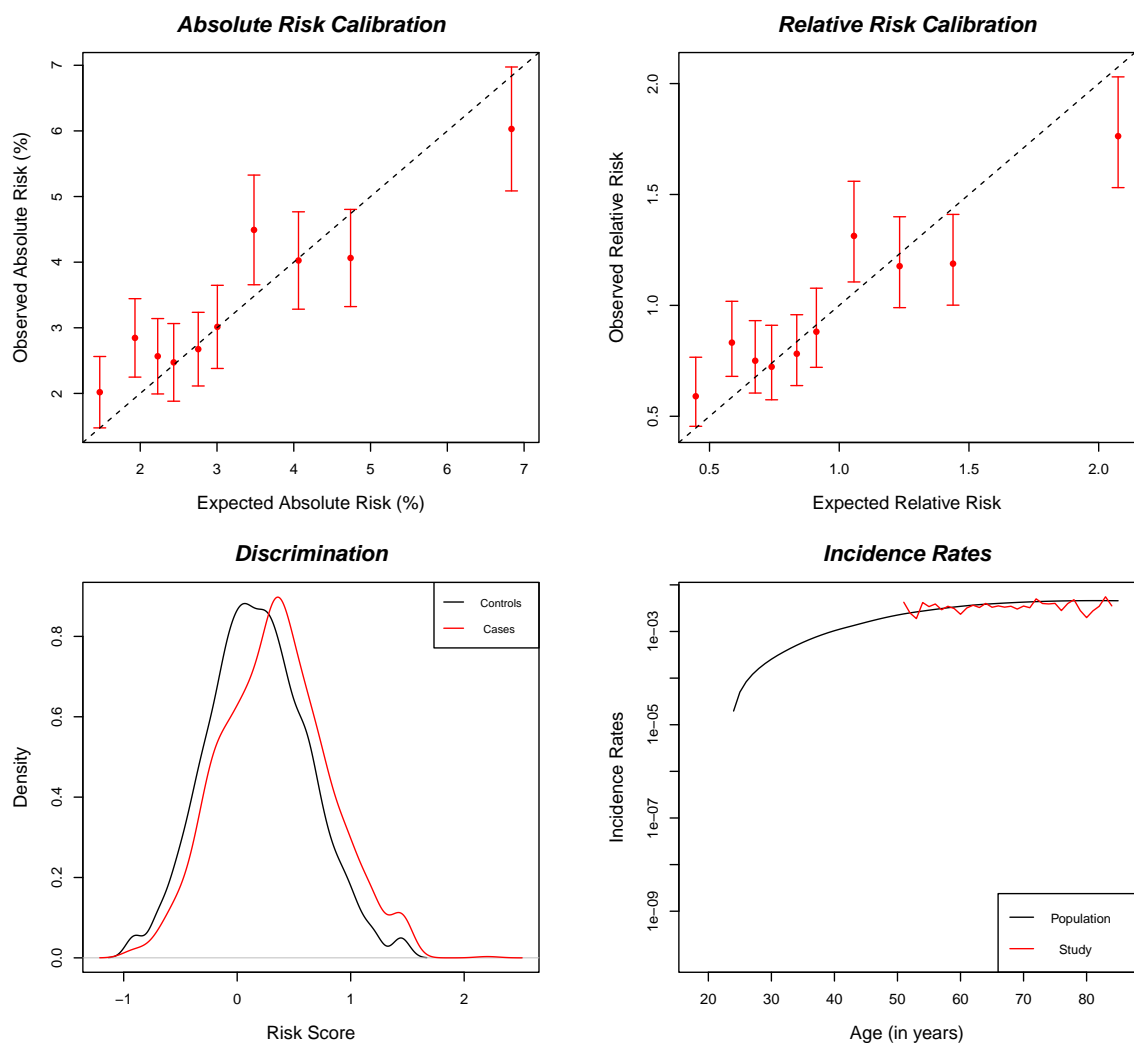
We can also produce a set of useful plots showing the results of the validation analysis.

```

> plotModelValidation(study.data = data, validation.results = output)

```

NULL



Dataset: Example Dataset

Model Name: Example Model

Risk Prediction Interval: Observed Followup

Number of subjects (cases): 5285 (1251)

Follow-up time (years) [mean,range]: [9.706 , (5 , 13)]

Baseline age (years) [mean,range]: [62.556 , (50 , 72)]

E/O [Estimate, 95% CI]: [0.967 , (0.908 , 1.03)]

Absolute Risk Calibration

HL Test, df: 25.925 , 10

p-value: 3.842949e-03

Relative Risk Calibration

Test, df: 35.528 , 9

p-value: 4.807e-05

Model Discrimination

AUC est: 0.587

95% CI: (0.568 , 0.605)

Session Information

```
> sessionInfo()
```

R version 4.1.1 (2021-08-10)

Platform: x86_64-w64-mingw32/x64 (64-bit)

Running under: Windows Server x64 (build 17763)

Matrix products: default

locale:

[1] LC_COLLATE=C

[2] LC_CTYPE=English_United States.1252

[3] LC_MONETARY=English_United States.1252

[4] LC_NUMERIC=C

[5] LC_TIME=English_United States.1252

attached base packages:

[1] stats graphics grDevices utils datasets methods base

other attached packages:

[1] iCARE_1.22.0 Hmisc_4.6-0 ggplot2_3.3.5 Formula_1.2-4

[5] survival_3.2-13 lattice_0.20-45 gtools_3.9.2 plotrix_3.8-2

loaded via a namespace (and not attached):

[1] tidyselect_1.1.1	xfun_0.27	purrr_0.3.4
[4] splines_4.1.1	colorspace_2.0-2	vctrs_0.3.8
[7] generics_0.1.1	htmltools_0.5.2	base64enc_0.1-3
[10] utf8_1.2.2	rlang_0.4.12	pillar_1.6.4
[13] foreign_0.8-81	glue_1.4.2	withr_2.4.2
[16] DBI_1.1.1	RColorBrewer_1.1-2	jpeg_0.1-9
[19] lifecycle_1.0.1	stringr_1.4.0	munsell_0.5.0
[22] gtable_0.3.0	htmlwidgets_1.5.4	latticeExtra_0.6-29
[25] knitr_1.36	fastmap_1.1.0	fansi_0.5.0
[28] htmlTable_2.3.0	scales_1.1.1	backports_1.2.1
[31] checkmate_2.0.0	gridExtra_2.3	png_0.1-7
[34] digest_0.6.28	stringi_1.7.5	dplyr_1.0.7
[37] grid_4.1.1	tools_4.1.1	magrittr_2.0.1
[40] tibble_3.1.5	cluster_2.1.2	crayon_1.4.1
[43] pkgconfig_2.0.3	ellipsis_0.3.2	Matrix_1.3-4
[46] data.table_1.14.2	assertthat_0.2.1	rstudioapi_0.13
[49] R6_2.5.1	rpart_4.1-15	nnet_7.3-16
[52] compiler_4.1.1		