iCARE (Individualized Coherent Absolute Risk Estimation) Package

April 28, 2026

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 
 13.022   0.108  13.133 
```

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)
```

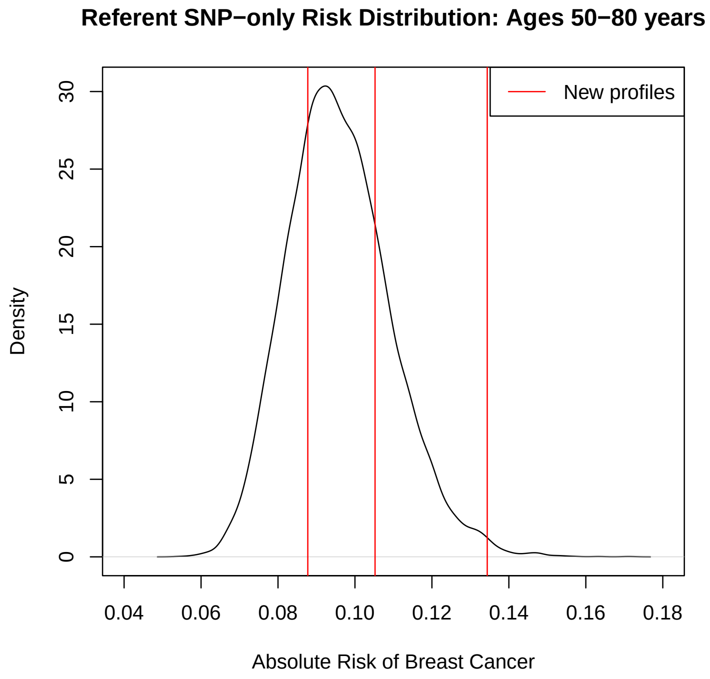
```
[1] "Note: As specified, the model does not adjust SNP imputations for family history."
   user  system elapsed
  0.340   0.034   0.375
```

```
> 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
  1.085   0.245   1.330
```

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 parity
1         1         1          0        0         0       0            8      0
2         1         0          0        0         0       0           10      0
3         0         0          0        0         0       0            1      0
  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 alcoholdweek_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.

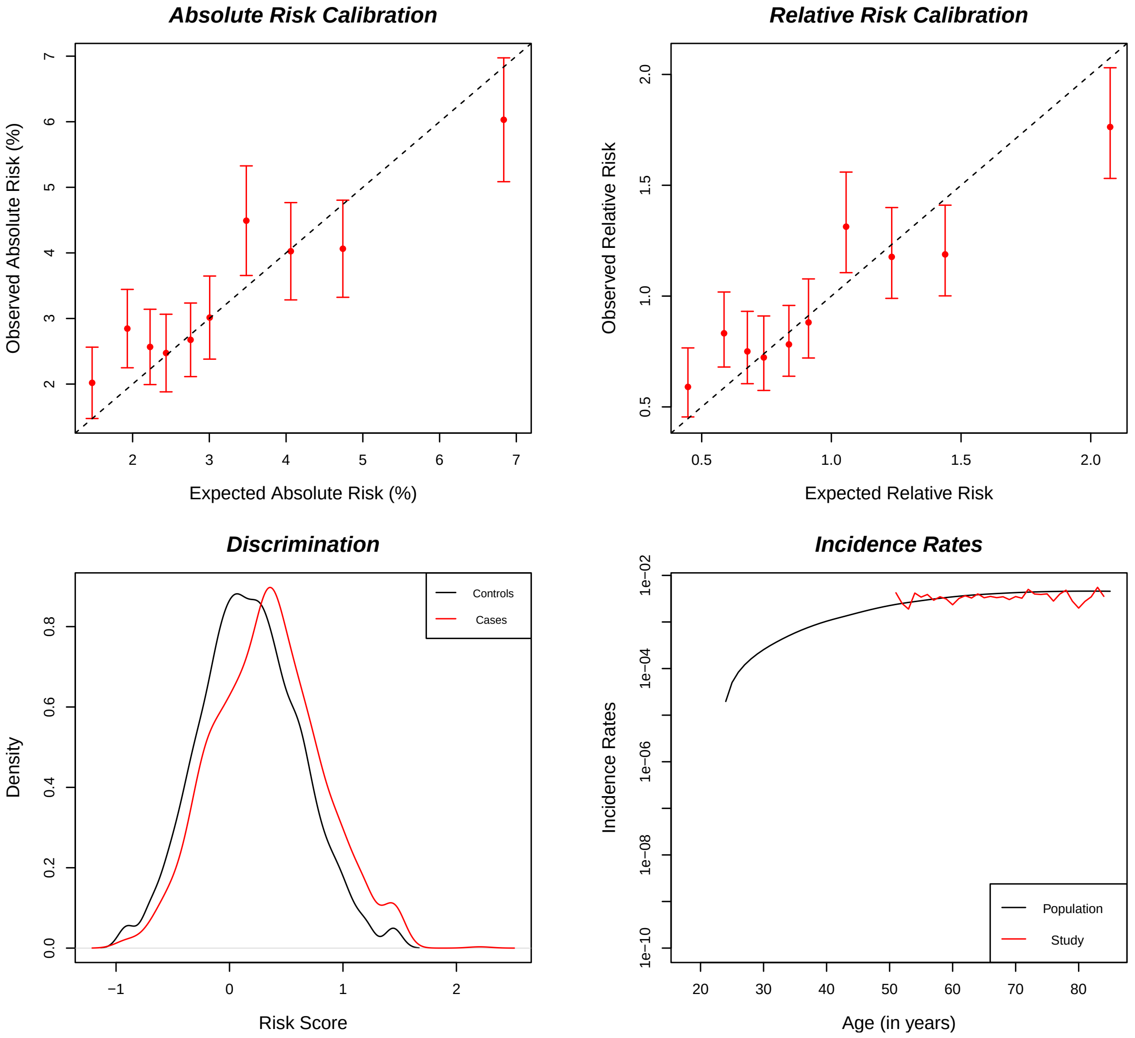
```
> data = validation.nested.case.control.data
> risk.model = list(model.formula = bc_model_formula,
+                   model.cov.info = bc_model_cov_info,
+                   model.snp.info = bc_72_snps,
+                   model.log.RR = bc_model_log_or,
+                   model.ref.dataset = ref_cov_dat,
+                   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
128.963   0.293 130.602
```

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	**Relative Risk Calibration**	**Model Discrimination**
HL Test, df: 25.925 , 10	Test, df: 35.528 , 9	AUC est: 0.587
p−value: 3.842949e−03	p−value: 4.807e−05	95% CI: (0.568 , 0.605)

Session Information

```
> sessionInfo()

R version 4.6.0 RC (2026-04-17 r89917)
Platform: x86_64-pc-linux-gnu
Running under: Ubuntu 24.04.4 LTS

Matrix products: default
BLAS:   /home/biocbuild/bbs-3.24-bioc/R/lib/libRblas.so
LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.12.0  LAPACK version 3.12.0

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
 [3] LC_TIME=en_GB              LC_COLLATE=C
 [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

time zone: America/New_York
tzcode source: system (glibc)

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
[1] iCARE_1.41.0   Hmisc_5.2-5    gtools_3.9.5   plotrix_3.8-14

loaded via a namespace (and not attached):
 [1] gtable_0.3.6       dplyr_1.2.1        compiler_4.6.0
 [4] rpart_4.1.27       tidyselect_1.2.1   htmlTable_2.5.0
 [7] stringr_1.6.0      dichromat_2.0-0.1  gridExtra_2.3
[10] cluster_2.1.8.2    scales_1.4.0       fastmap_1.2.0
[13] ggplot2_4.0.3      R6_2.6.1           generics_0.1.4
[16] Formula_1.2-5      knitr_1.51         htmlwidgets_1.6.4
[19] backports_1.5.1    checkmate_2.3.4    tibble_3.3.1
[22] nnet_7.3-20        pillar_1.11.1      RColorBrewer_1.1-3
[25] rlang_1.2.0        stringi_1.8.7      xfun_0.57
[28] S7_0.2.2           otel_0.2.0         cli_3.6.6
[31] magrittr_2.0.5     digest_0.6.39      grid_4.6.0
[34] rstudioapi_0.18.0  base64enc_0.1-6    lifecycle_1.0.5
[37] vctrs_0.7.3        data.table_1.18.2.1 evaluate_1.0.5
[40] glue_1.8.1         farver_2.1.2       colorspace_2.1-2
[43] rmarkdown_2.31     foreign_0.8-91     tools_4.6.0
[46] pkgconfig_2.0.3    htmltools_0.5.9
```