Supplementary Materials for "ROCnReg: An R Package for Receiver Operating Characteristic Curve Inference with and without Covariates"

María Xosé Rodríguez-Álvarez and Vanda Inácio

This document contains supplementary materials to the paper "ROCnReg: An R Package for Receiver Operating Characteristic Curve Inference with and without Covariates". In Web Appendix A, we provide a detailed description of the frequentist methods implemented in the `R`-package **ROCnReg** (`https://CRAN.R-project.org/package=ROCnReg`) for the estimation of the pooled ROC, covariate-specific ROC curve, and covariate-adjusted ROC curve. In Web Appendix B, Web Appendix C, and Web Appendix D, we illustrate their usage. Also in these sections, we provide further (informal) model diagnostics and convergence assessments for the Bayesian methods described and illustrated in the main manuscript.

Web Appendix A Frequentist methods for ROC curve inference implemented in ROCnReg

In this section we describe the different frequentist methods for ROC inference (with and without covariates) implemented in the **ROCnReg** package.

A1 Pooled ROC curve

Let $\{y_{\bar{D}i}\}_{i=1}^{n_{\bar{D}}}$ and $\{y_{Dj}\}_{j=1}^{n_D}$ be two independent random samples of test outcomes from the nondiseased and diseased groups of size $n_{\bar{D}}$ and n_D, respectively.

A1.1 Empirical estimator

The function `pooledROC.emp` estimates the pooled ROC curve using the empirical estimator proposed by Hsieh and Turnbull (1996), which consists in estimating the CDFs of the test in each group by its empirical counterpart, that is,

$$\widehat{F}_{\bar{D}}(y) = \frac{1}{n_{\bar{D}}}\sum_{i=1}^{n_{\bar{D}}} I(y_{\bar{D}i} \leq y), \qquad \widehat{F}_{D}(y) = \frac{1}{n_{D}}\sum_{j=1}^{n_{D}} I(y_{Dj} \leq y).$$

These empirical estimates are then plugged into Equations (1) and (6) in the main paper to obtain, respectively, an estimate of the ROC and ROC_{TNF} curves.

In what concerns estimation of the AUC (Equation (3) in the main paper), pAUC, and pAUC_{TNF} (Equations (4) and (5) in the main paper) these are computed empirically by means of the Mann–Whitney U statistic.

María Xosé Rodríguez-Álvarez, BCAM-Basque Center for Applied Mathematics & IKERBASQUE, Basque Foundation for Science, Bilbao, Basque Country, Spain (*mxrodriguez@bcamath.org*). Vanda Inácio, School of Mathematics, University of Edinburgh, Scotland, UK (*vanda.inacio@ed.ac.uk*).

With respect to the Youden index (and associated threshold value), it is obtained by maximizing, over a grid of possible threshold values, the expression in (8) in the main paper, with F_D and $F_{\bar{D}}$ being replaced by their empirical estimators.

A1.2 Kernel estimator

The function `pooledROC.kernel` estimates the pooled ROC curve using the kernel-based estimator proposed by Zou et al. (1997) and Zou et al. (1998), which is based on estimating the CDFs of the test as follows

$$\widehat{F}_{\bar{D}}(y) = \frac{1}{n_{\bar{D}}}\sum_{i=1}^{n_{\bar{D}}}\Phi\left(\frac{y - y_{\bar{D}i}}{h_{\bar{D}}}\right), \qquad \widehat{F}_{D}(y) = \frac{1}{n_{D}}\sum_{j=1}^{n_{D}}\Phi\left(\frac{y - y_{Dj}}{h_{D}}\right),$$

where $\Phi(y)$ stands for the standard normal distribution evaluated at y. For the bandwidths, $h_{\bar{D}}$ and h_D, which control the amount of smoothing, two options are popular. Silverman's rule of thumb (Silverman, 1986, p. 48), which sets the bandwidth as

$$h_d = 0.9\min\{\mathrm{SD}(\mathbf{y}_d), \mathrm{IQR}(\mathbf{y}_d)/1.34\}n_d^{-0.2}, \quad d \in \{\bar{D}, D\},$$

where $\mathrm{SD}(\mathbf{y}_d)$ and $\mathrm{IQR}(\mathbf{y}_d)$ are the standard deviation and interquantile range, respectively, of $\mathbf{y}_d = (y_{d1}, \ldots, y_{dn_d})$. Another alternative criterion is to select the bandwidth by using least squares cross-validation (Wand and Jones, 1994, Chapter 3).

Here, both the AUC, pAUC, and $\mathrm{pAUC}_{\mathrm{TNF}}$ (Equations (2), (4), and (5) in the main paper) are computed numerically using Simpson's rule. Regarding the Youden Index (and associated threshold value), it is obtained by maximizing, over a grid of possible threshold values, Expression (8) in the main paper, with F_D and $F_{\bar{D}}$ being replaced by their kernel estimators.

Uncertainty estimation for both the empirical and kernel estimators is conducted through bootstrap resampling and the resampling can be done both with or without regard to the disease status.

A2 Covariate-specific ROC curve

As in the main paper, let $\{(\mathbf{x}_{\bar{D}i}, y_{\bar{D}i})\}_{i=1}^{n_{\bar{D}}}$ and $\{(\mathbf{x}_{Dj}, y_{Dj})\}_{j=1}^{n_D}$ be two independent random samples of test outcomes and covariates from the nondiseased and diseased groups of size $n_{\bar{D}}$ and n_D, respectively. Further, for all $i = 1, \ldots, n_{\bar{D}}$ and $j = 1, \ldots, n_D$, let $\mathbf{x}_{\bar{D}i} = (x_{\bar{D}i,1}, \ldots, x_{\bar{D}i,q})^{\top}$ and $\mathbf{x}_{Dj} = (x_{Dj,1}, \ldots, x_{Dj,q})^{\top}$ be q-dimensional vectors of covariates, which can be either continuous or categorical.

A2.1 Induced semiparametric linear model

The function `cROC.sp` implements the induced ROC approaches proposed by Faraggi (2003) and Pepe (1998). Both authors assume a location-scale regression model of the following form for the test outcomes in each group

$$Y_{\bar{D}} = \tilde{\mathbf{X}}_{\bar{D}}^{\top}\boldsymbol{\beta}_{\bar{D}} + \sigma_{\bar{D}}\varepsilon_{\bar{D}}, \qquad Y_D = \tilde{\mathbf{X}}_{D}^{\top}\boldsymbol{\beta}_{D} + \sigma_{D}\varepsilon_{D}, \tag{A1}$$

where $\tilde{\mathbf{X}}_{\bar{D}}^{\top} = (1, \mathbf{X}_{\bar{D}}^{\top})$ and $\boldsymbol{\beta}_{\bar{D}} = (\beta_{\bar{D}0}, \ldots, \beta_{\bar{D}q})^{\top}$ is a $(q+1)$-dimensional vector of (unknown) regression coefficients; $\tilde{\mathbf{X}}_D$ and $\boldsymbol{\beta}_D$ are analogously defined. The error terms $\varepsilon_{\bar{D}}$ and ε_D have mean zero, variance one, are independent of each other and of the covariates, and have distribution functions given by $F_{\varepsilon_{\bar{D}}}$ and F_{ε_D}, respectively. Under these assumptions, we have

$$F_{\bar{D}}(y \mid \mathbf{x}) = F_{\varepsilon_{\bar{D}}}\left(\frac{y - \tilde{\mathbf{x}}^{\top}\boldsymbol{\beta}_{\bar{D}}}{\sigma_{\bar{D}}}\right) \quad \text{and} \quad F_{D}(y \mid \mathbf{x}) = F_{\varepsilon_{D}}\left(\frac{y - \tilde{\mathbf{x}}^{\top}\boldsymbol{\beta}_{D}}{\sigma_{D}}\right), \tag{A2}$$

with $\tilde{\mathbf{x}}^\top = (1, \mathbf{x}^\top)$.

The approaches of Faraggi (2003) and Pepe (1998) differ in the assumptions made about the error terms. More concretely, Faraggi (2003)'s method assumes that the error term in both groups follows a standard normal distribution, i.e., $F_{\varepsilon_{\bar{D}}}(y) = F_{\varepsilon_D}(y) = \Phi(y)$, and can be summarized by the following three steps:

1. Estimate the regression coefficients $\boldsymbol{\beta}_{\bar{D}}$ and $\boldsymbol{\beta}_D$ by ordinary least squares, on the basis of the samples $\{(\mathbf{x}_{\bar{D}i}, y_{\bar{D}i})\}_{i=1}^{n_{\bar{D}}}$ and $\{(\mathbf{x}_{Dj}, y_{Dj})\}_{j=1}^{n_D}$, respectively.

2. Estimate $\widehat{\sigma}_D^2$ as
$$\widehat{\sigma}_D^2 = \frac{\sum_{j=1}^{n_D}\left(y_{Dj} - \tilde{\mathbf{x}}_{Dj}^\top\widehat{\boldsymbol{\beta}}_D\right)^2}{n_D - q - 1},$$
with $\widehat{\sigma}_{\bar{D}}^2$ similarly estimated.

3. For a given covariate vector $\mathbf{x}$, compute the covariate-specific ROC curve as follows
$$\widehat{\text{ROC}}(p \mid \mathbf{x}) = 1 - \Phi\left\{a(\mathbf{x}) + b\Phi^{-1}(1-p)\right\}, \tag{A3}$$
where
$$a(\mathbf{x}) = \tilde{\mathbf{x}}^\top\frac{\left(\widehat{\boldsymbol{\beta}}_{\bar{D}} - \widehat{\boldsymbol{\beta}}_D\right)}{\widehat{\sigma}_D}, \quad \text{and} \quad b = \frac{\widehat{\sigma}_{\bar{D}}}{\widehat{\sigma}_D}. \tag{A4}$$

Regarding the covariate-specific AUC, pAUC, and pAUC_{TPF} (Expressions (12), (13), and (14) in the main paper) they admit closed-form expressions (see Hillis and Metz, 2012).

As an alternative, Pepe (1998) suggests to estimate the CDF of the errors in each group by the corresponding empirical CDF of the estimated standardized residuals. Therefore, the first two steps of the estimation procedure remain the same, but now we have the following extra step

$$\widehat{F}_{\varepsilon_D}(y) = \frac{1}{n_D}\sum_{j=1}^{n_D} I(\widehat{\varepsilon}_{Dj} \leq y), \qquad \widehat{\varepsilon}_{Dj} = \frac{y_{Dj} - \tilde{\mathbf{x}}_{Dj}^\top\widehat{\boldsymbol{\beta}}_D}{\widehat{\sigma}_D}.$$

The empirical CDF of the standardized residuals in the nondiseased group is estimated in a similar fashion. The covariate-specific ROC curve is finally computed in an analogous way as for the method of Faraggi (2003) as
$$\widehat{\text{ROC}}(p \mid \mathbf{x}) = 1 - \widehat{F}_{\varepsilon_D}\left\{a(\mathbf{x}) + b\widehat{F}_{\varepsilon_{\bar{D}}}^{-1}(1-p)\right\}.$$

Here, the covariate-specific AUC and pAUC (Expressions (12) and (13) in the main paper) also admit closed forms. However, especially for large datasets, their calculation can be very time-consuming. As a consequence, in **ROCnReg** they are computed numerically using Simpson's rule; in our experience Simpson's rule provides almost identical results to the ones obtained using the closed-form expressions. In what concerns the covariate-specific pAUC_{TNF}, it is interesting to note that

$$\widehat{\text{ROC}}_{\text{TNF}}(p \mid \mathbf{x}) = 1 - \widehat{F}_{\varepsilon_D}\left\{a^*(\mathbf{x}) + b^*\widehat{F}_{\varepsilon_{\bar{D}}}^{-1}(1-p)\right\},$$

with

$$a^*(\mathbf{x}) = \tilde{\mathbf{x}}^\top\frac{\left(\widehat{\boldsymbol{\beta}}_D - \widehat{\boldsymbol{\beta}}_{\bar{D}}\right)}{\widehat{\sigma}_{\bar{D}}} \quad \text{and} \quad b^* = \frac{\widehat{\sigma}_D}{\widehat{\sigma}_{\bar{D}}}.$$

The covariate-specific $\mathrm{pAUC}_{\mathrm{TNF}}$ (Expression (14) in the main paper), although it also admits a closed form expression, for the reasons mentioned before, is computed numerically using Simpson's rule based on the expressions given above.

Finally, in pretty much the same way as for the pooled ROC curve, the covariate-specific Youden index (and associated threshold value) is obtained by maximizing, over a grid of possible threshold values, the expression in (16) (main paper), making use of result (A2).

A2.2 Induced kernel-based approach

The kernel-based approach of González-Manteiga et al. (2011) and Rodríguez-Álvarez et al. (2011) is available in the `cROC.kernel` function. Differently to all the other estimating approaches for the covariate-specific ROC curve covered in **ROCnReg**, it can only deal with one continuous covariate. Similarly to the approaches of Pepe (1998) and Faraggi (2003), it also assumes a location-scale regression model for the test outcomes in each group, but the effect of the covariate is not assumed to be linear and the variance is allowed to depend on the covariate. Specifically, the models postulated in each group are as follows

$$Y_{\bar{D}} = \mu_{\bar{D}}(X_{\bar{D}}) + \sigma_{\bar{D}}(X_{\bar{D}})\varepsilon_{\bar{D}}, \qquad Y_D = \mu_D(X_D) + \sigma_D(X_D)\varepsilon_D, \tag{A5}$$

where $\mu_D(x) = \mathrm{E}(Y_D \mid X_D = x)$ and $\sigma_D^2(x) = \mathrm{Var}(Y_D \mid X_D = x)$ are the regression and variance functions, respectively, with $\mu_{\bar{D}}(x)$ and $\sigma_{\bar{D}}^2(x)$ being analogously defined. The error terms $\varepsilon_{\bar{D}}$ and ε_D have mean zero, variance one, are independent of each other and of the covariate, and have distribution functions given by $F_{\varepsilon_{\bar{D}}}$ and F_{ε_D}, respectively.

Both the regression and variance functions are estimated using local polynomial kernel smoothers (Fan and Gijbels, 1996). In particular, local constant (Nadaraya–Watson) or local linear estimators are employed for the regression function, whereas for the variance function only local constant estimators are used. Estimation in **ROCnReg** makes use of the `R` package `np` by Hayfield and Racine (2008). We note that estimation proceeds in a sequential manner: 1) the regression function, say in the diseased group, is estimated first on the basis of $\{(x_{Dj}, y_{Dj})\}_{j=1}^{n_D}$ and denote the corresponding estimate by $\widehat{\mu}_D$, and 2) the variance function is estimated next on the basis of the sample $\{(x_{Dj}, [y_{Dj} - \widehat{\mu}_D(x_{Dj})]^2)\}$. Both steps involve the selection of a bandwidth parameter which is done via cross-validation. As in the model of Pepe (1998), the CDFs F_{ε_D} and $F_{\varepsilon_{\bar{D}}}$ are estimated via the empirical CDF of the standardized residuals, that is,

$$\widehat{F}_{\varepsilon_D}(y) = \frac{1}{n_D}\sum_{j=1}^{n_D} I(\widehat{\varepsilon}_{Dj} \leq y), \qquad \widehat{\varepsilon}_{Dj} = \frac{y_{Dj} - \widehat{\mu}_D(x_{Dj})}{\widehat{\sigma}_D(x_{Dj})},$$

with the empirical CDF of the standardized residuals in the nondiseased group estimated analogously. Finally, the covariate-specific ROC curve is computed in an analogous way as before as

$$\widehat{\mathrm{ROC}}(p \mid x) = 1 - \widehat{F}_{\varepsilon_D}\left\{a(x) + b(x)\widehat{F}_{\varepsilon_{\bar{D}}}^{-1}(1-p)\right\},$$

where

$$a(x) = \frac{\widehat{\mu}_{\bar{D}}(x) - \widehat{\mu}_D(x)}{\widehat{\sigma}_D(x)} \quad \text{and} \quad b(x) = \frac{\widehat{\sigma}_{\bar{D}}(x)}{\widehat{\sigma}_D(x)}.$$

Estimation of the covariate-specific AUC, pAAUC, $\mathrm{pAUC}_{\mathrm{TNF}}$, and YI follows a similar reasoning as the one described previously for the induced semiparametric linear model when no assumptions are made regarding the distribution of the error terms.

For both the induced semiparametric linear model and the induced kernel approach, uncertainty quantification is done through a bootstrap of the residuals. For further details see, for instance, Rodríguez-Álvarez et al. (2011).

A3 Covariate-adjusted ROC curve

All estimators for the covariate-adjusted ROC curve make use of the following expression (Equation (19) in the main paper)

$$\mathrm{AROC}(p) = \Pr\left\{1 - F_{\bar{D}}(Y_D \mid \mathbf{X}_D) \leq p\right\},$$

and rely on the following three steps

1. Estimation of the conditional distribution of test outcomes in the nondiseased group, $F_{\bar{D}}(y_{\bar{D}i} \mid \mathbf{x}_{\bar{D}i})$.
2. Computation of the placement value $U_D = 1 - F_{\bar{D}}(Y_D \mid \mathbf{X}_D)$ where, by a slight abuse of notation, we are designating it by the same letter used for the unconditional case.
3. Estimation of the cumulative distribution function of U_D.

The approaches used for estimation of the AROC curve proposed by Janes and Pepe (2009) and Rodríguez-Álvarez et al. (2011) only differ in Step 1. Specifically, once one has an estimate of the conditional CDF in the nondiseased group, say $\widehat{F}_{\bar{D}}(\cdot \mid \mathbf{x})$, Step 2 in the two approaches consists of trivially computing the diseased placement values as

$$\widehat{U}_{Dj} = 1 - \widehat{F}_{\bar{D}}(y_{Dj} \mid \mathbf{x}_{Dj}), \quad j = 1, \ldots, n_D.$$

Next, in Step 3, the AROC curve at a false positive fraction of p is estimated via the empirical distribution function of the placement values calculated in the previous step, $\{\widehat{U}_{Dj}\}_{j=1}^{n_D}$, that is,

$$\widehat{\mathrm{AROC}}(p) = \frac{1}{n_D}\sum_{j=1}^{n_D} I(\widehat{U}_{Dj} \leq p).$$

With regard to Step 1, both authors assume a location-scale regression model for the test outcomes in the nondiseased group and, as such and as explained in the previous section, the conditional CDF of the test results can be written using the CDF of the regression errors, i.e.,

$$F_{\bar{D}}(y \mid \mathbf{x}) = F_{\varepsilon_{\bar{D}}}\left(\frac{y - \mu_{\bar{D}}(\mathbf{x})}{\sigma_{\bar{D}}(\mathbf{x})}\right).$$

While Janes and Pepe (2009) assume a location-scale model of the form of (A1), Rodríguez-Álvarez et al. (2011) rely on specification (A5). The estimation of the mean and variance functions follow exactly the same procedures as those described in the induced semiparametric linear model (for Janes and Pepe 2009) and in the induced kernel-based approach (for Rodríguez-Álvarez et al. 2011) for the covariate specific ROC curve (the only difference being that here we only need to perform the estimation for the nondiseased group). At last, and also as in the estimators for the covariate-specific ROC curve, $F_{\varepsilon_{\bar{D}}}$ can be either assumed to be the standard normal distribution or left unspecified and estimated empirically on the basis of the standardized residuals. In both cases, the AAUC and pAAUC can be computed as follows

$$\widehat{\mathrm{AAUC}} = \int_0^1 \widehat{\mathrm{AROC}}(p)\mathrm{d}p = 1 - \frac{1}{n_D}\sum_{j=1}^{n_D}\widehat{U}_{Dj},$$

$$\mathrm{p}\widehat{\mathrm{AAUC}(u_1)} = \int_0^{u_1} \widehat{\mathrm{AROC}}(p)\mathrm{d}p = u_1 - \frac{1}{n_D}\sum_{j=1}^{n_D}\min\left\{u_1, \widehat{U}_{Dj}\right\},$$

whereas the $\mathrm{pAAUC}_{\mathrm{TNF}}$ is computed as in Equation (22) of the main paper using numerical integration methods (function `integrate` in `R` package `stats`).

Web Appendix B Further computational tools for the pooled ROC curve

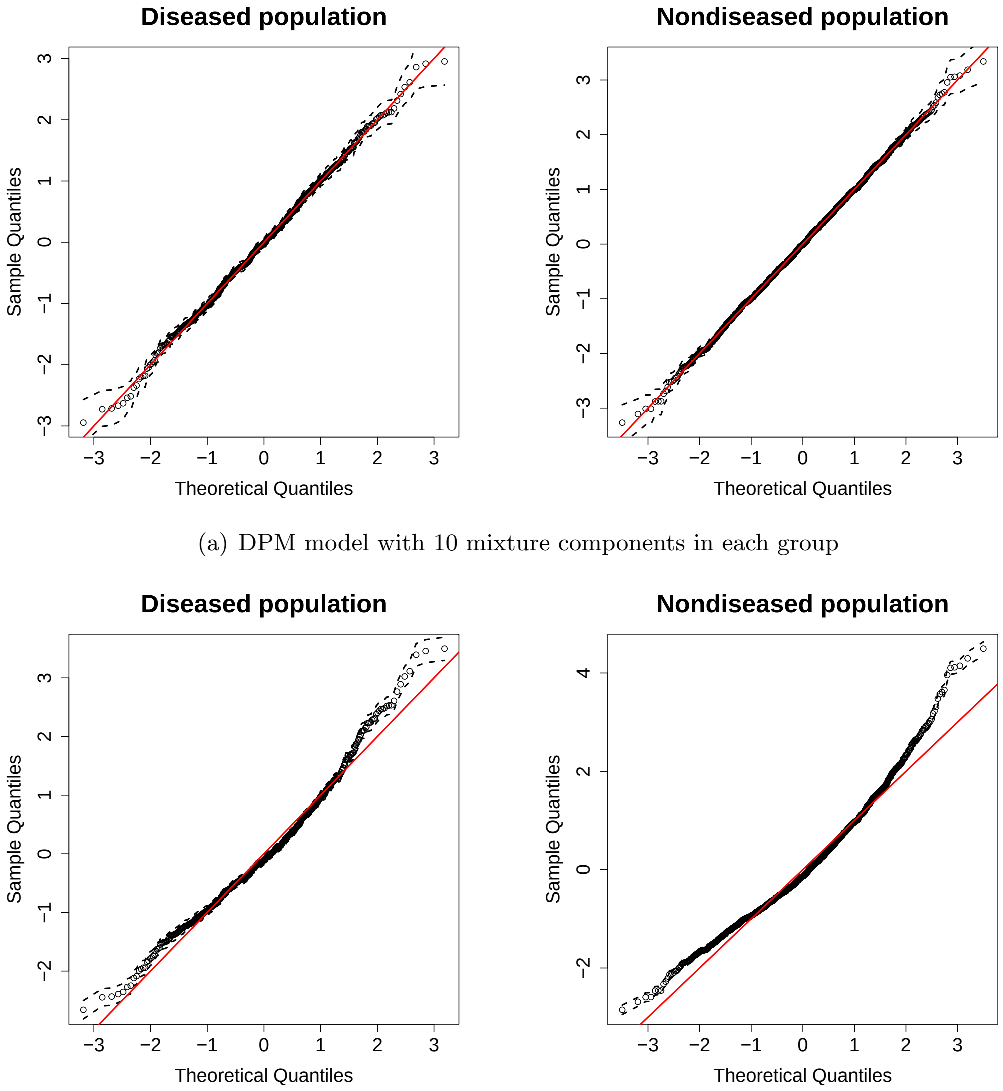
B1 Informal model diagnostics for the Bayesian methods: quantile residuals

We illustrate the use of quantile residuals (Dunn and Smyth, 1996) which can be helpful for models fitted using the function `pooledROC.dpm`, for instance, in deciding if $L_D = 1$ or $L_D > 1$ (the same obviously applies to the nondiseased group). Quantile residuals are based on the well-known fact that for a continuous random variable, say Y_D, with CDF given by F_D, one has that $F_D(Y_D) \sim \mathrm{U}(0,1)$. As a consequence, quantile residuals defined by $\widehat{r}_{Dj} = \Phi^{-1}\{\widehat{F}_D(y_{Dj})\}$, for $j = 1, \ldots, n_D$, should follow, approximately, a standard normal distribution if a correct model has been specified. A quantile-quantile (QQ) plot can then be used to determine deviations of the quantile residuals from the standard normal distribution. Below we provide the code to construct, for the diseased population, such QQ plot using output from the object `pROC_dpm` (that assumed $L_D = L_{\bar{D}} = 10$) obtained using the function `pooledROC.dpm`. The code for the nondiseased population follows in a similar manner, and is provided in the `R` replication code that accompanies this paper.

```r
library(ROCnReg)
library(nor1mix)
data("endosyn")

set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
pROC_dpm <- pooledROC.dpm(marker = "bmi", group = "cvd_idf",
                          tag.h = 0, data = endosyn,
                          standardise = TRUE, p = seq(0, 1, l = 101), ci.level = 0.95,
                          compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
                          pauc = pauccontrol(compute = TRUE, focus = "FPF", value = 0.1),
                          density = densitycontrol(compute = TRUE),
                          prior.h = priorcontrol.dpm(L = 10),
                          prior.d = priorcontrol.dpm(L = 10),
                          mcmc = mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1),
                          parallel = "snow", ncpus = 2)

# Quantile residuals (diseased population)
traj <- matrix(0, nrow = pROC_dpm$mcmc$nsave, ncol = length(pROC_dpm$marker$d))
lgrid <- length(pROC_dpm$marker$d)
grid <- qnorm(ppoints(lgrid))
for (l in 1:pROC_dpm$mcmc$nsave) {
  aux <- norMix(mu = pROC_dpm$fit$d$mu[l,], sigma = pROC_dpm$fit$d$sd[l,],
              w = pROC_dpm$fit$d$probs[l,])
  traj[l, ] <- quantile(qnorm(pnorMix(pROC_dpm$marker$d, aux)), ppoints(lgrid), type = 2)
}
l.band_d <- apply(traj, 2, quantile, prob = 0.025)
trajhat_d <- apply(traj, 2, mean)
u.band_d <- apply(traj, 2, quantile, prob = 0.975)

op <- par(pty = "s")
plot(grid, trajhat_d, xlab = "Theoretical Quantiles", ylab = "Sample Quantiles",
     main = "Diseased population", cex.main = 2, cex.lab = 1.5, cex.axis = 1.5)
lines(grid, l.band_d, lty = 2, lwd = 2)
lines(grid, u.band_d, lty = 2, lwd = 2)
abline(a = 0, b = 1, col ="red", lwd = 2)
par(op)
```

The resulting QQ plots are shown in Figure 1(a) and show virtually no deviations from the standard normal distribution quantiles, thus revealing a good fit of the DPM model that assumes 10 mixture components in both the diseased and nondiseased groups. In contrast, those QQ plots obtained when fitting a normal model in each group (i.e., $L_D = L_{\bar{D}} = 1$; model `pROC_normal` in the main manuscript), clearly show some deviations from the assumed normal distribution quantiles (see Figure 1(b)). The code used follows

```
pROC_normal <- pooledROC.dpm(marker = "bmi", group = "cvd_idf",
                             tag.h = 0, data = endosyn,
                             standardise = TRUE, p = seq(0, 1, l = 101), ci.level = 0.95,
                             compute.lpml = TRUE, compute.WAIC = TRUE, compute.DIC = TRUE,
                             pauc = pauccontrol(compute = TRUE, focus = "FPF", value = 0.1),
                             density = densitycontrol(compute = TRUE),
                             prior.h = priorcontrol.dpm(L = 1),
                             prior.d = priorcontrol.dpm(L = 1),
                             mcmc = mcmccontrol(nsave = 8000, nburn = 2000, nskip = 1),
                             parallel = "snow", ncpus = 2)

# Quantile residuals (diseased population)
traj_normal <- matrix(0, nrow = pROC_normal$mcmc$nsave, ncol = length(pROC_normal$marker$d))
for (l in 1:pROC_normal$mcmc$nsave) {
  traj_normal[l, ] <- quantile(qnorm(pnorm(pROC_normal$marker$d,pROC_normal$fit$d$mu[l],
                                            pROC_normal$fit$d$sd[l])),
                               ppoints(lgrid), type = 2)
}
l.band_normal_d <- apply(traj_normal, 2, quantile, prob = 0.025)
trajhat_normal_d <- apply(traj_normal, 2, mean)
u.band_normal_d <- apply(traj_normal, 2, quantile, prob = 0.975)

op <- par(pty = "s")
plot(grid, trajhat_normal_d, xlab = "Theoretical Quantiles", ylab = "Sample Quantiles",
     main = "Diseased population", cex.main = 2, cex.lab = 1.5, cex.axis = 1.5)
lines(grid, l.band_normal_d, lty = 2, lwd = 2)
lines(grid, u.band_normal_d, lty = 2, lwd = 2)
abline(a = 0, b = 1, col ="red", lwd = 2)
par(op)
```



(a) DPM model with 10 mixture components in each group

(b) Normal model in each group

Web Figure 1: Quantile residuals of the BMI data versus the theoretical quantiles of the standard normal distribution. The circles represent the posterior mean quantiles over all posterior samples, while the dashed lines represent the corresponding 95% credible bands. Top row: DPM model with 10 components in each group (model `pROC_dpm` in the main manuscript). Bottom row: normal model in each group (model `pROC_normal` in the main manuscript).

B2 Empirical and kernel estimators of the pooled ROC curve

The following code is used to fit the empirical ROC curve estimator for the pooled ROC curve (function `pooledROC.emp`). The number of bootstrap resamples is `B = 500` and, for the sake of illustration, we also compute the partial area under the curve corresponding to true positive fractions between 0.8 and 1.

```r
library(ROCnReg)
data(endosyn)
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
pROC_emp <- pooledROC.emp(marker = "bmi", group = "cvd_idf",
                          tag.h = 0, data = endosyn,
                          p = seq(0, 1, l = 101),
                          pauc = pauccontrol(compute = TRUE, focus = "TPF", value = 0.8),
                          B = 500, ci.level = 0.95,
                          parallel = "snow", ncpus = 2)
summary(pROC_emp)
```

```
##
## Call:
## pooledROC.emp(marker = "bmi", group = "cvd_idf", tag.h = 0, data = endosyn,
##     p = seq(0, 1, l = 101), B = 500, ci.level = 0.95, pauc = pauccontrol(compute = TRUE,
##         focus = "TPF", value = 0.8), parallel = "snow", ncpus = 2)
##
## Approach: Pooled ROC curve - Empirical
## ----------------------------------------------
## Area under the pooled ROC curve: 0.76 (0.743, 0.778)*
## Partial area under the specificity pooled ROC curve (Se = 0.8): 0.423 (0.387, 0.46)*
##  * Confidence level:  0.95
##
## Sample sizes:
##                            Group H     Group D
## Number of observations        2149         691
## Number of missing data           0           0
```

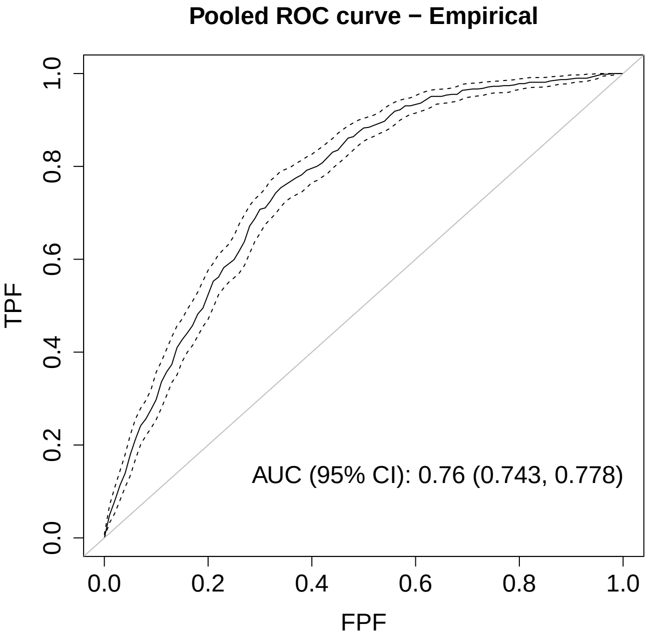
Note that all partial areas' values returned are normalized and, as such, what is being reported in this case is

$$\mathrm{pAUC}_{\mathrm{TPF}}(0.8)/(1-0.8).$$

The estimated pooled ROC curve and AUC, jointly with 95% bootstrap confidence intervals, are obtained as follows.

```r
plot(pROC_emp, cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5, cex = 1.5)
```

The result is shown in Figure 2.



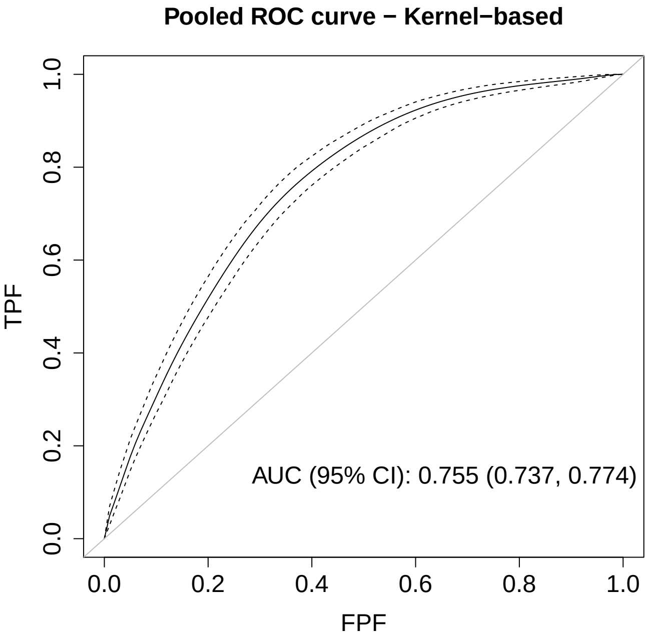
Web Figure 2: Graphical results as provided by the `plot.pooledROC` function for an object of class `pooledROC.emp`. Estimate and 95% pointwise bootstrap confidence band of the pooled ROC curve and corresponding estimated AUC (and 95% confidence interval).

We shall present now the syntax associated to the kernel estimator of the pooled ROC curve (function `pooledROC.kernel`). In terms of arguments, `bw` specifies how the bandwidth should be computed, with `SRT` standing for Silverman's rule of thumb and `UCV` for least squares cross-validation. Additionally, `B` stands for the number of bootstrap replications used to compute the confidence intervals/bands. The code follows.

```
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
pROC_kernel <- pooledROC.kernel(marker = "bmi", group = "cvd_idf",
                                tag.h = 0, data = endosyn,
                                p = seq(0, 1, l = 101),
                                bw = "SRT",
                                B = 500, ci.level = 0.95,
                                method = "coutcome",
                                pauc = pauccontrol(compute = TRUE, focus = "TPF", value = 0.8),
                                parallel = "snow", ncpus = 2)
summary(pROC_kernel)

##
## Call:
## pooledROC.kernel(marker = "bmi", group = "cvd_idf", tag.h = 0,
##     data = endosyn, p = seq(0, 1, l = 101), bw = "SRT", B = 500,
##     ci.level = 0.95, method = "coutcome", pauc = pauccontrol(compute = TRUE,
##         focus = "TPF", value = 0.8), parallel = "snow", ncpus = 2)
##
## Approach: Pooled ROC curve - Kernel-based
## ----------------------------------------------
## Area under the pooled ROC curve: 0.755 (0.737, 0.774)*
## Partial area under the specificity pooled ROC curve (Se = 0.8): 0.408 (0.373, 0.446)*
##  * Confidence level:  0.95
##
##                 Group H     Group D
## Bandwidths:       0.867       1.019
##
##
##
## Bandwidth Selection Method: Silverman's rule-of-thumb
##
## Sample sizes:
##                            Group H     Group D
## Number of observations        2149         691
## Number of missing data           0           0
```

Graphical results are obtained with the following code, and presented in Figure 3.

```
plot(pROC_kernel, cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5, cex = 1.5)
```

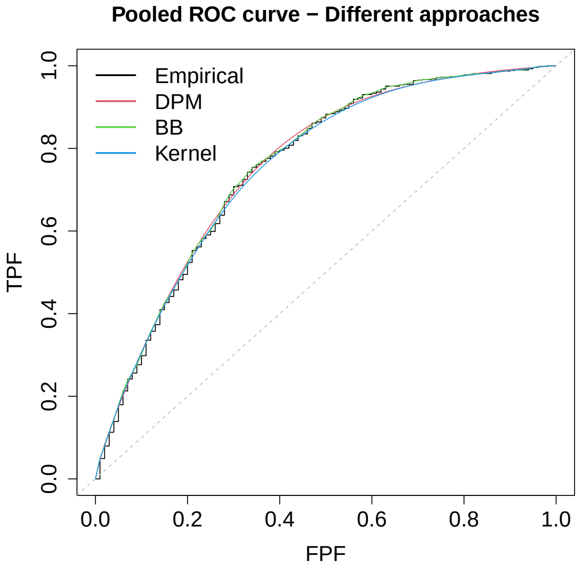


Web Figure 3: Graphical results as provided by the `plot.pooledROC` function for an object of class `pooledROC.kernel`. Estimate and 95% pointwise bootstrap confidence interval of the pooled ROC curve and corresponding AUC.

B3 Comparison of pooled ROC curve estimates

We finish with a comparison of the estimated pooled ROC curves obtained using all methods incorporated in **ROCnReg** to do so: `pooledROC.dpm`, `pooledROC.BB`, `pooledROC.emp`, and `pooledROC.kernel`. To make the code reproducible, we first estimate the ROC curve using the Bayesian bootstrap approach. Results are shown in Figure 4.

```
# Bayesian bootstrap
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
pROC_BB <- pooledROC.BB(marker = "bmi", group = "cvd_idf", tag.h = 0, data = endosyn,
      p = seq(0, 1, l = 101), B = 5000, ci.level = 0.95, parallel = "snow", ncpus = 2)

# Comparisons
plot(pROC_emp$p, pROC_emp$ROC[,1], type = "s", xlim = c(0,1), ylim = c(0,1), xlab = "FPF",
     ylab = "TPF", main = "Pooled ROC curve - Different approaches",
     cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5)
lines(pROC_dpm$p, pROC_dpm$ROC[,1], col = 2)
lines(pROC_BB$p, pROC_BB$ROC[,1], col = 3)
lines(pROC_kernel$p, pROC_kernel$ROC[,1], col = 4)
abline(0, 1, col = "grey", lty = 2)
legend("topleft", legend = c("Empirical", "DPM", "BB", "Kernel"), lty = 1, col = 1:4,
       bty = "n", lwd = 2, cex = 1.5)
```

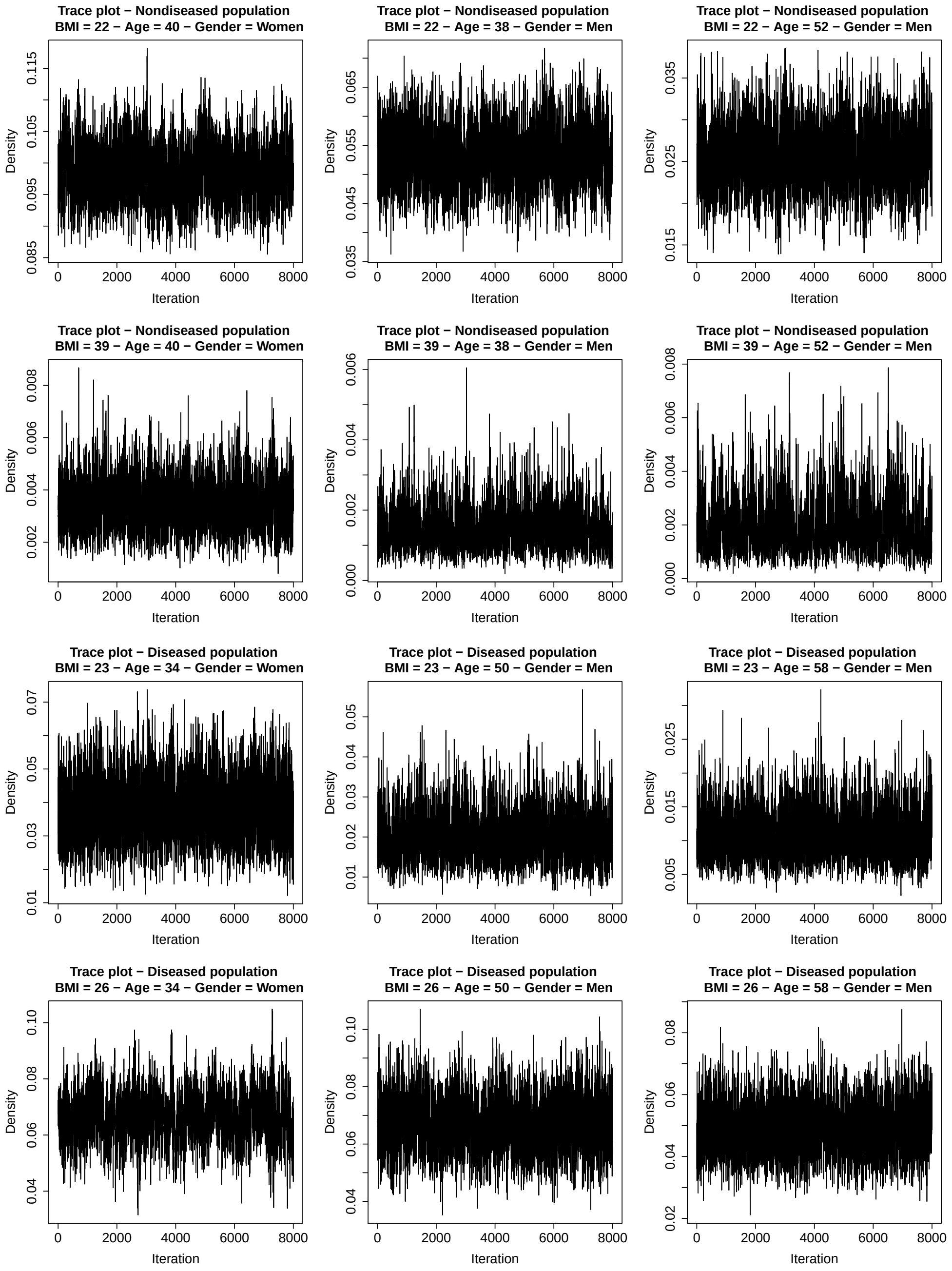


Web Figure 4: ROC curve estimated using the different approaches implemented in **ROCnReg**. ‘Empirical’ stands for the empirical estimator, ‘DPM’ for the Dirichlet process mixture of normal distributions estimator, ‘BB’ for the Bayesian bootstrap approach, and ‘Kernel’ for the kernel estimator.

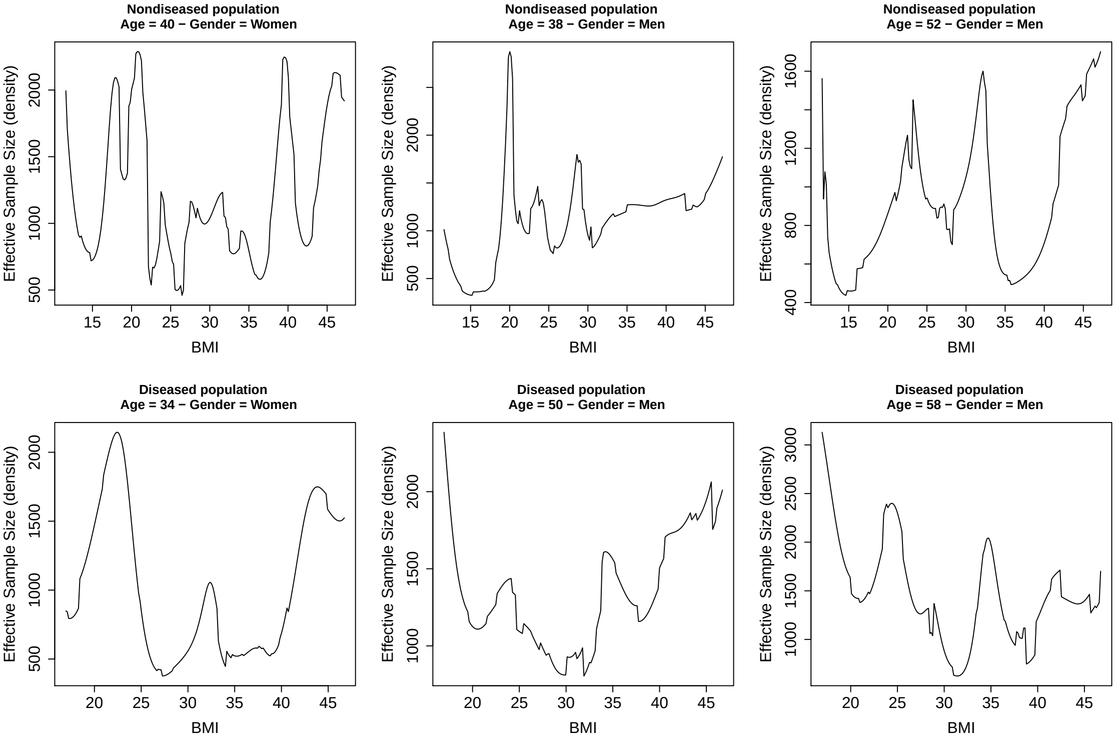
Web Appendix C Further computational tools for the covariate-specific ROC curve

C1 Convergence assessments for the Bayesian methods: trace plots, effective sample sizes, and Geweke statistics

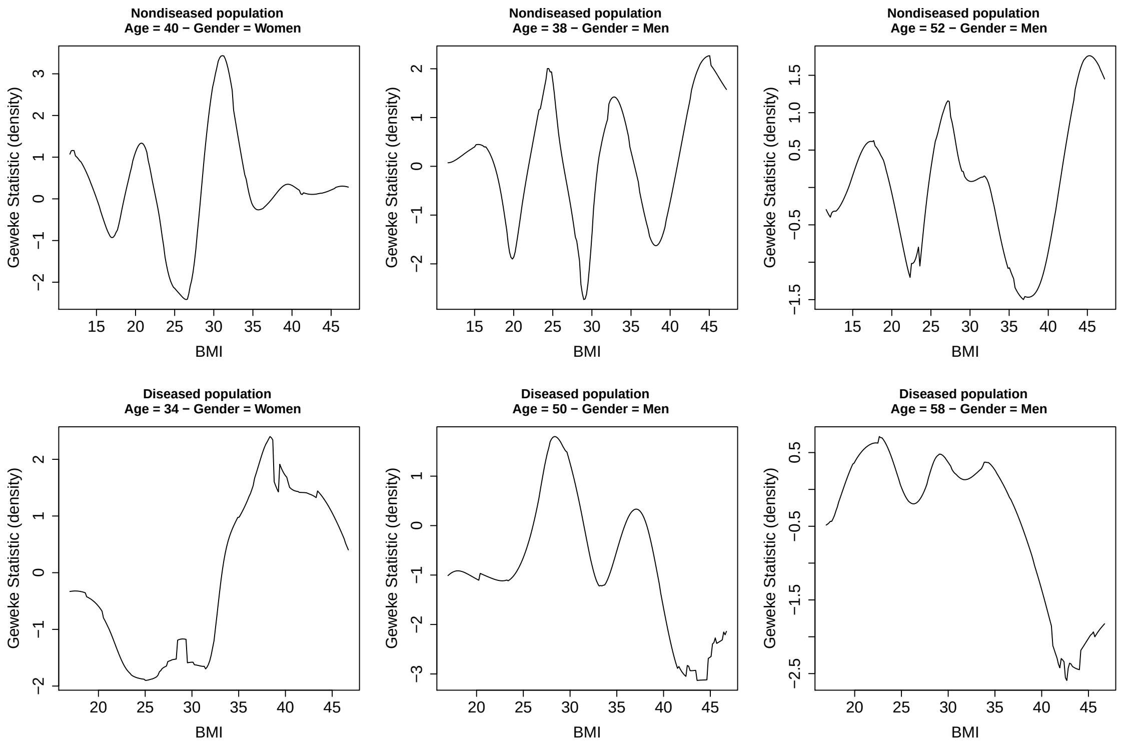
We start by including, for model `cROC_bnp` in Section "Package presentation and illustration" of the main manuscript, some trace plots of the MCMC draws (after burn-in) of the conditional PDFs of BMI (Figure 5) and corresponding effective sample sizes and Geweke statistics (Figure 6 and 7, respectively). All plots show good mixing of the MCMC chains and do not suggest lack of convergence. For conciseness, the `R`-code for producing Figures 5, 6, and 7 is not provided here, but in the `R` replication code that accompanies this paper.



Web Figure 5: Trace plots of the MCMC draws (after burn-in) of the conditional PDFs of BMI based on model cROC_bnp. Results are shown separately for the nondiseased and diseased population, for different combinations of age and gender (covariates) and for different values of the BMI.



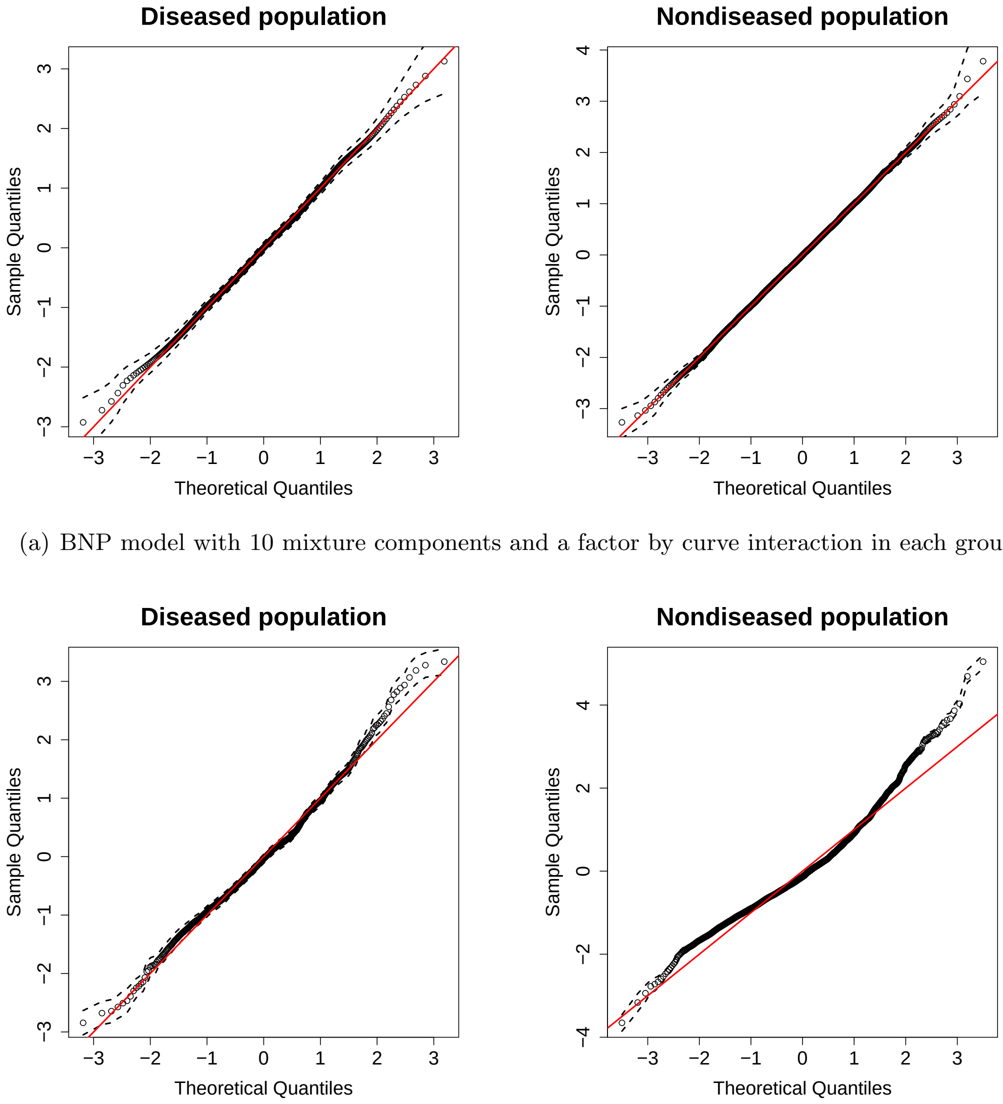
Web Figure 6: Effective sample size of the MCMC chains (after burn-in) of the conditional PDFs of BMI based on model `pROC_dpm`. Results are shown separately for the nondiseased and diseased population and for different combinations of `age` and `gender`. In all cases, results are shown along BMI values.



Web Figure 7: Geweke statistic of the MCMC chains (after burn-in) of the conditional PDFs of BMI based on model `cROC_bnp`. Results are shown separately for the nondiseased and diseased population and for different combinations of `age` and `gender`. In all cases, results are shown along BMI values.

C2 Informal model diagnostics for the Bayesian methods: quantile residuals and conditional densities

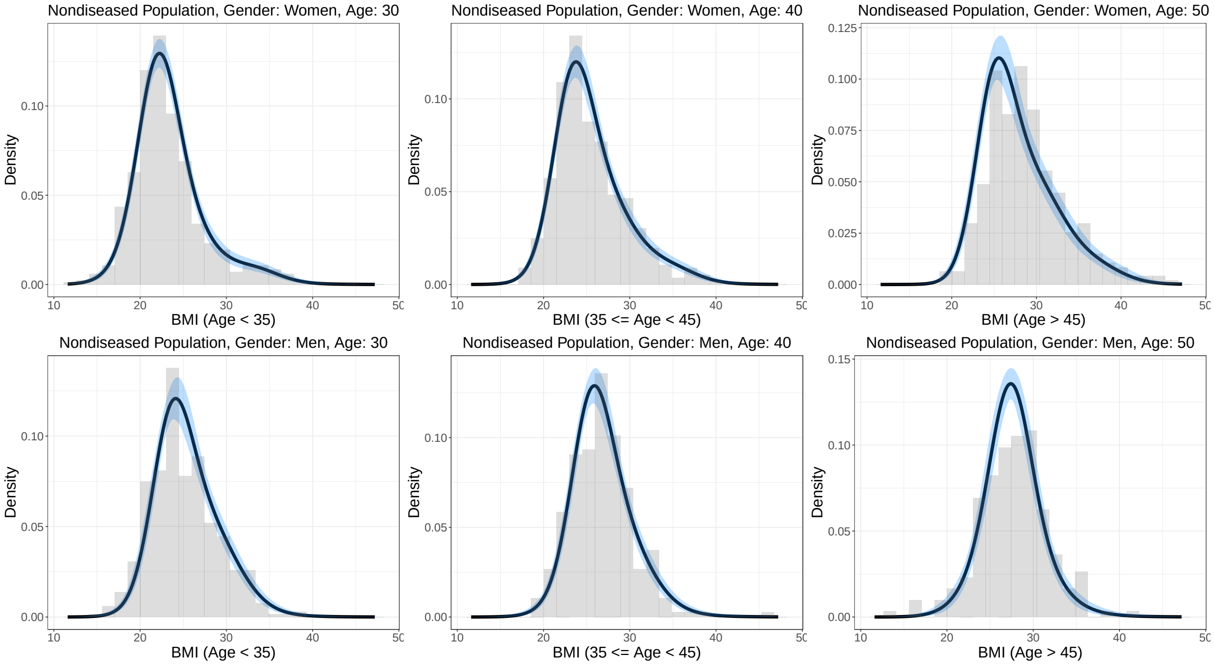
As in the no covariates case, we also present the quantile residuals for both the Bayesian normal linear model (designated as model `cROC_bp` in Section "Package presentation and illustration" of the main manuscript) and for the Bayesian nonparametric model with 10 mixture components and a factor by curve interaction (model `cROC_bnp` in the main text). The results are shown in Figure 8 and, as for the unconditional case, they show virtually no deviation from the quantiles of the standard normal distribution, in both the diseased and nondiseased groups, for the Bayesian nonparametric method. Further, in Figures 9 and 10 we also show the histograms of the BMI for selected age intervals and for both men and women, along with the estimated (by model `cROC_bnp`) conditional distribution of BMI given age and gender, in the nondiseased and diseased groups. As it can be appreciated, the estimated conditional densities follow quite nicely the histograms of the BMI for the different age intervals and genders. For conciseness, the `R`-code for producing these figures is not provided here, but in the `R` replication code that accompanies the paper.



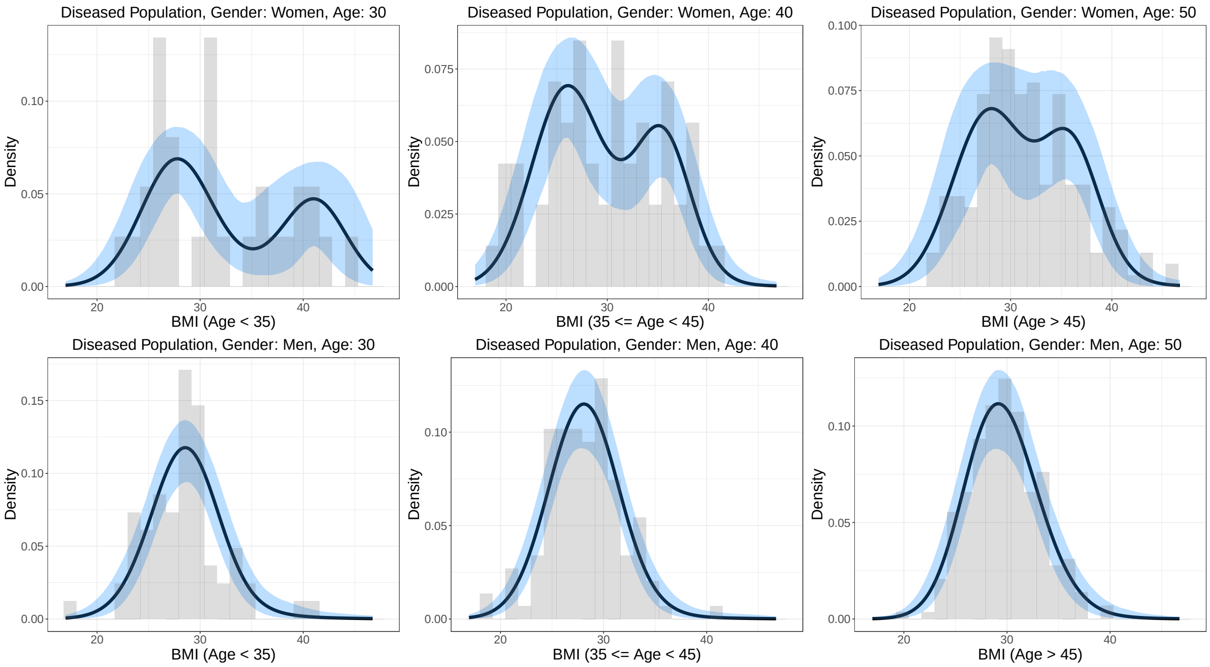
(a) BNP model with 10 mixture components and a factor by curve interaction in each group

(b) Bayesian normal linear model in each group

Web Figure 8: Quantile residuals of the BMI data versus the theoretical quantiles of the standard normal distribution. The circles represent the posterior mean quantiles over all posterior samples, while the dashed lines represent the corresponding 95% credible bands. Top row: BNP model with 10 mixture components and a factor by curve interaction in each group (model `cROC_bnp` in the main manuscript). Bottom row: Bayesian normal linear model in each group (model `cROC_bp` in the main manuscript).



Web Figure 9: Histograms of the BMI for selected age intervals and for men and women, along with the pointwise mean (continuous blue lines) and 95% credible bands (shaded blue areas) for the conditional distribution of BMI given age and gender, in the nondiseased group, under the BNP model with 10 mixture components and a factor by curve interaction. The ages of 30, 40, and 50 correspond, respectively and approximately, to the 25th, 50th, and 75th percentiles of the age variable in the whole dataset.



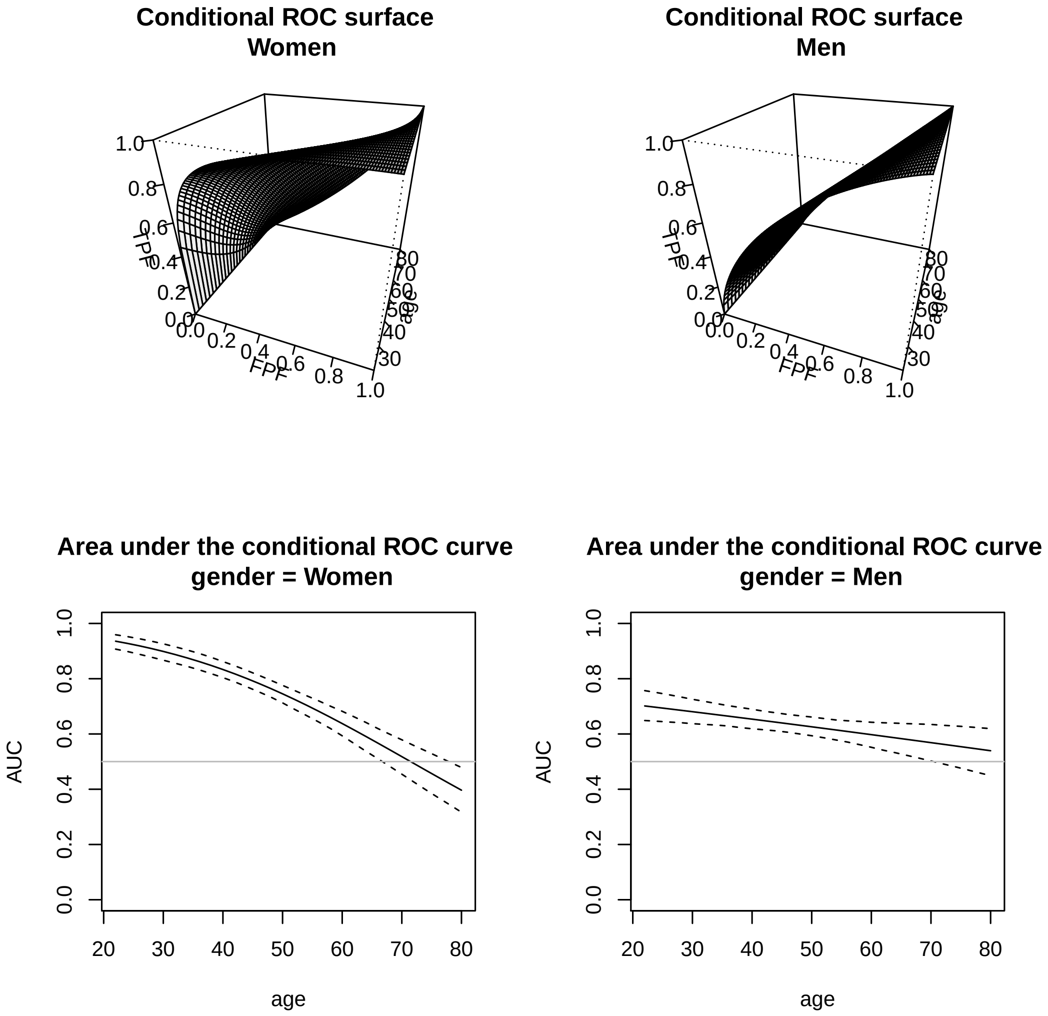
Web Figure 10: Histograms of the BMI for selected age intervals and for men and women, along with the pointwise mean (continuous blue lines) and 95% credible bands (shaded blue areas) for the conditional distribution of BMI given age and gender, in the diseased group, under the BNP model with 10 mixture components and a factor by curve interaction. The ages of 30, 40, and 50 correspond, respectively and approximately, to the 25th, 50th, and 75th percentiles of the age variable in the whole dataset.

C3 Frequentist estimators of the covariate-specific ROC curve

We now turn our attention on how to estimate the covariate-specific ROC curve using the induced (semiparametric) linear model (function `cROC.sp`). As for the Bayesian linear model described in the main manuscript, for both the nondiseased and diseased groups, the model for the regression functions includes, in addition to the linear effect of `age` and `gender`, the (linear) interaction between the two (i.e., `gender*age` ≡ `gender + age + gender:age`). Also, by specifying `est.cdf = "normal"`, we assume that the error term in both groups follows a standard normal distribution. Finally, uncertainty estimation for this method is based on the bootstrap, and through argument `B`, we indicate the number of resamples. As usual, numeric and graphical summaries are obtained using, respectively, the functions `summary` and `plot` (see Figure 11).

```
require(ROCnReg)
data(endosyn)
# Data frame for predictions
agep <- seq(22, 80, l = 30)
endopred <- data.frame(age = rep(agep,2),
                       gender = factor(rep(c("Women", "Men"), each = length(agep))))

set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
cROC_sp <- cROC.sp(formula.h = bmi ~ gender*age,
                   formula.d = bmi ~ gender*age,
                   group = "cvd_idf",
                   tag.h = 0,
                   data = endosyn,
                   newdata = endopred,
                   est.cdf = "normal",
                   p = seq(0, 1, l = 101),
                   B = 500, ci.level = 0.95,
                   parallel = "snow", ncpus = 2)

summary(cROC_sp)

##
## Call:
## cROC.sp(formula.h = bmi ~ gender * age, formula.d = bmi ~ gender *
##     age, group = "cvd_idf", tag.h = 0, data = endosyn, newdata = endopred,
##     est.cdf = "normal", p = seq(0, 1, l = 101), B = 500, ci.level = 0.95,
##     parallel = "snow", ncpus = 2)
##
## Approach: Conditional ROC curve - semiparametric
## ----------------------------------------------------------
##
## Parametric coefficients
## Group H:
##                    Estimate    Quantile 2.5%    Quantile 97.5%
## (Intercept)         22.7670          21.9331           23.5509
## genderWomen         -4.2942          -5.2247           -3.3091
## age                  0.0885           0.0680            0.1091
## genderWomen:age      0.0885           0.0645            0.1124
##
##
## Group D:
##                    Estimate    Quantile 2.5%    Quantile 97.5%
## (Intercept)         26.9171          25.5389           28.2935
## genderWomen          4.7363           2.2900            7.1651
## age                  0.0440           0.0161            0.0719
## genderWomen:age     -0.0515          -0.0954           -0.0075
##
##
## ROC curve:
##                    Estimate    Quantile 2.5%    Quantile 97.5%
## (Intercept)         -0.9482          -1.3376           -0.6040
## genderWomen         -2.0633          -2.6498           -1.4612
## age                  0.0102           0.0026            0.0183
## genderWomen:age      0.0320           0.0191            0.0442
## b                    0.9378           0.8728            1.0044
##
##
## Model selection criteria:
##           Group H     Group D
## AIC     12173.673    4007.215
## BIC     12202.037    4029.905
##
##
```

```
## Sample sizes:
##                            Group H     Group D
## Number of observations        2149         691
## Number of missing data           0           0
```



Web Figure 11: Graphical results as provided by the `plot.cROC` function for an object of class `cROC.sp`. Results for a model that includes the linear interaction between `age` and `gender`. Top row: Estimate of the covariate-specific ROC curve along age, separately for men and women. Bottom row: Estimate and 95% pointwise bootstrap confidence interval of the covariate-specific AUC along age, separately for men and women.

When it comes to estimating the covariate-specific ROC curve using the induced kernel-based approach (function `cROC.kernel`), we should keep in mind that it can only deal with one continuous covariate. As a consequence, and for our synthetic endocrine data, we evaluate the `age` effect separately for men and women, i.e., we fit two different models. The code follows. Note that in contrast with the other functions for estimating the covariate-specific ROC curve, the function `cROC.kernel` expects the arguments `marker` and `covariate`, where the user specifies, respectively, the name of the variables that contain the test results (in our example `bmi`) and the covariate (`age`). Uncertainty estimation for this method is also based on the bootstrap, and through the argument `B`, we indicate the number of resamples. Numeric and graphical summaries are obtained using, respectively, the functions `summary` and `plot`. The graphical results, for both men and women, are shown in Figure 12.

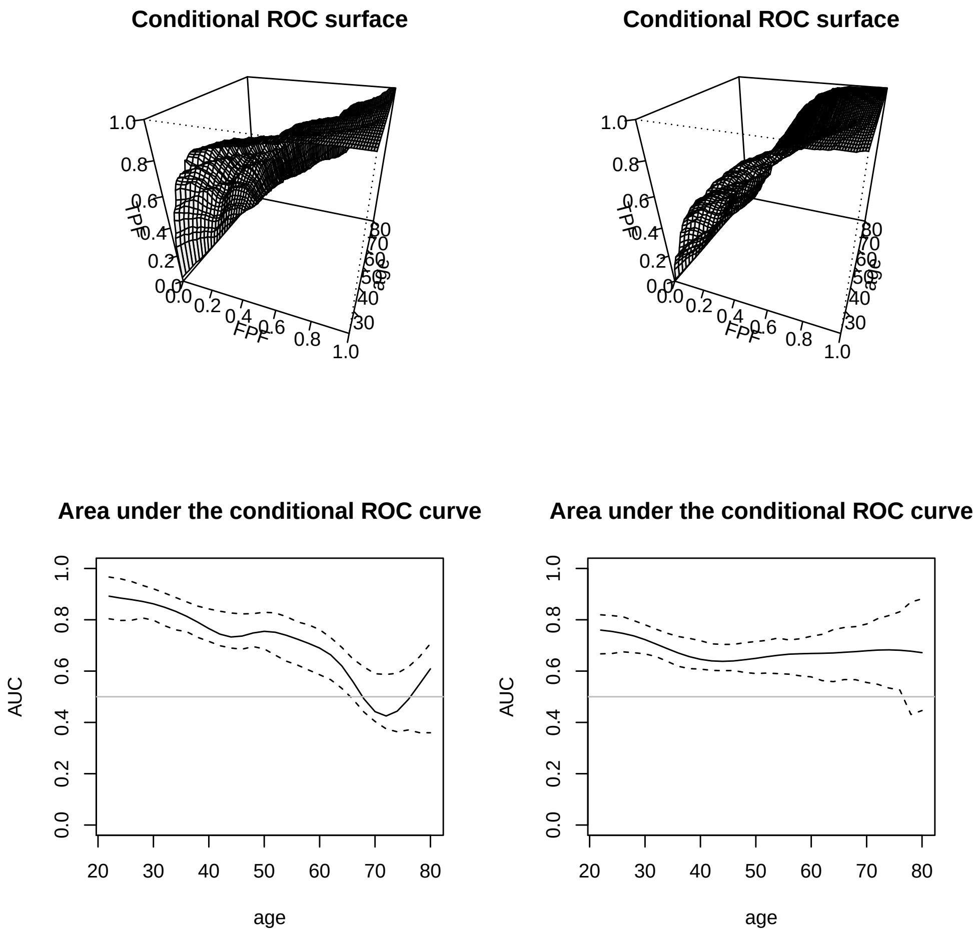
```r
require(ROCnReg)
options(np.messages = FALSE)
data(endosyn)
agep <- seq(22, 80, l = 30)
endopred_ker <- data.frame(age = agep)

# Men
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
cROC_kernel_men <- cROC.kernel(marker = "bmi",
                               covariate = "age",
                               group = "cvd_idf",
                               tag.h = 0,
                               data = subset(endosyn, gender == "Men"),
                               newdata = endopred_ker,
                               p = seq(0, 1, l = 101),
                               B = 500,
                               ci.level = 0.95,
                               parallel = "snow", ncpus = 2)

summary(cROC_kernel_men)

##
## Call:
## cROC.kernel(marker = "bmi", covariate = "age", group = "cvd_idf",
##     tag.h = 0, data = subset(endosyn, gender == "Men"), newdata = endopred_ker,
##     p = seq(0, 1, l = 101), B = 500, ci.level = 0.95, parallel = "snow",
##     ncpus = 2)
##
## Approach: Conditional ROC curve - Kernel-based
## ----------------------------------------------------------
##
## Regression functions:
##
##                  Group H      Group D
## Bandwidth:     5.767820     6.477821
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Variance functions:
##
##                  Group H       Group D
## Bandwidth:     6.489771     18.567326
```

```
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Sample sizes:
##                             Group H     Group D
## Number of observations          899         418
## Number of missing data            0           0
```

```
# Women
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
cROC_kernel_women <- cROC.kernel(marker = "bmi",
                                 covariate = "age",
                                 group = "cvd_idf",
                                 tag.h = 0,
                                 data = subset(endosyn, gender == "Women"),
                                 newdata = endopred_ker,
                                 p = seq(0, 1, l = 101),
                                 B = 500,
                                 ci.level = 0.95,
                                 parallel = "snow", ncpus = 2)

summary(cROC_kernel_women)
```

```
##
## Call:
## cROC.kernel(marker = "bmi", covariate = "age", group = "cvd_idf",
##     tag.h = 0, data = subset(endosyn, gender == "Women"), newdata = endopred_ker,
##     p = seq(0, 1, l = 101), B = 500, ci.level = 0.95, parallel = "snow",
##     ncpus = 2)
##
## Approach: Conditional ROC curve - Kernel-based
## ----------------------------------------------------------
##
## Regression functions:
##
##                  Group H      Group D
## Bandwidth:     3.993242     4.308757
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Variance functions:
##
##                   Group H       Group D
## Bandwidth:     18.250812     10.490069
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
```

```
##
## Sample sizes:
##                             Group H     Group D
## Number of observations        1250         273
## Number of missing data           0           0

op <- par(mfcol = c(2,2))
plot(cROC_kernel_women, ask = FALSE)
plot(cROC_kernel_men, ask = FALSE)
par(op)
```



Web Figure 12: Graphical results as provided by the `plot.cROC` function for an object of class `cROC.kernel`. Top row: Estimate of the covariate-specific ROC curve along age, separately for men (left) and women (right). Bottom row: Estimate and 95% pointwise bootstrap confidence interval of the covariate-specific AUC along age, separately for men (left) and women (right). Results in this case were obtained separately for men and women.

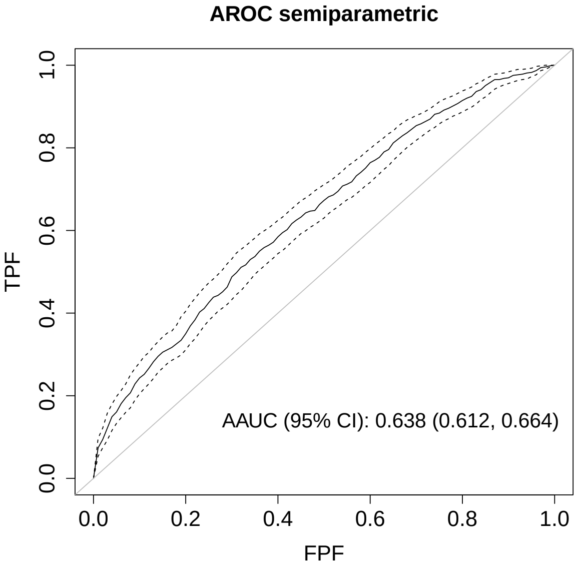
Web Appendix D Further computational tools for the covariate-adjusted ROC curve

D1 Frequentist estimators of the AROC curve

We finish presenting the code for estimating the covariate-adjusted ROC curve (AROC curve) using the induced semiparametric linear model (function `AROC.sp`) and the kernel-based approach (function `AROC.kernel`). We avoid giving many details, and simply present the code for fitting the models and obtaining the numerical and graphical summaries. It is important to note that, since the kernel-based approach only deals with one continuous covariate, the AROC curve in this case is estimated separately in men and women. This is to be differentiated from the AROC curve obtained by including both `age` and `gender`, which reflects the discriminatory capacity solely due to the `bmi` while teasing out both the `age` and `gender` effects. The code for the estimator of Janes and Pepe (2009) follows and the corresponding graphical result is shown in Figure 13.

```
require(ROCnReg)
data(endosyn)
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
AROC_sp <- AROC.sp(formula.h = bmi ~ gender*age,
                   group = "cvd_idf",
                   tag.h = 0,
                   data = endosyn,
                   est.cdf = "normal",
                   p = seq(0, 1, l = 101),
                   B = 500,
                   ci.level = 0.95,
                   parallel = "snow", ncpus = 2)

summary(AROC_sp)

##
## Call:
## AROC.sp(formula.h = bmi ~ gender * age, group = "cvd_idf", tag.h = 0,
##     data = endosyn, est.cdf.h = "normal", p = seq(0, 1, l = 101),
##     B = 500, ci.level = 0.95, parallel = "snow", ncpus = 2)
##
## Approach: AROC semiparametric
## ----------------------------------------------
## Area under the covariate-adjusted ROC curve: 0.638 (0.612, 0.664)*
##  * Confidence level:  0.95
##
## Parametric coefficients (Group H):
##                      Estimate    Quantile 2.5%    Quantile 97.5%
## (Intercept)           22.7670          22.0029           23.6441
## genderWomen           -4.2942          -5.4177           -3.3017
## age                    0.0885           0.0658            0.1080
## genderWomen:age        0.0885           0.0637            0.1147
##
##
## Model selection criteria:
##            Group H
## AIC     12173.673
## BIC     12202.037
```

```
##
##
## Sample sizes:
##                               Group H     Group D
## Number of observations          2149         691
## Number of missing data             0           0

plot(AROC_sp, cex.main = 1.5, cex.lab = 1.5, cex.axis = 1.5, cex = 1.3)
```

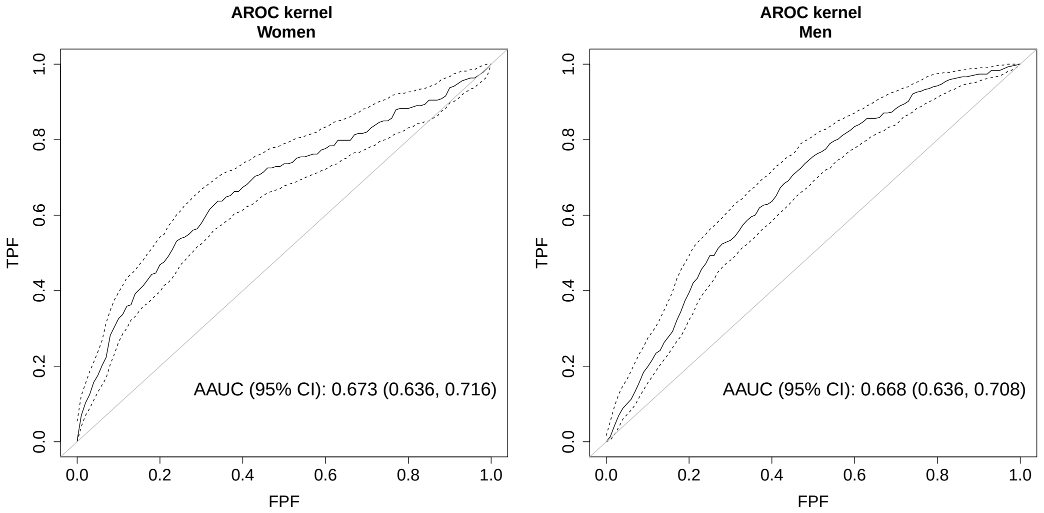


Web Figure 13: Graphical results as provided by the `plot.AROC` function for an object of class `AROC.sp`. Estimate and 95% pointwise bootstrap confidence interval of the age and gender adjusted ROC curve (AROC) and corresponding AUC.

We now show th code for the kernel estimator of Rodríguez-Álvarez et al. (2011) and the graphical results are shown in Figure 14.

```
options(np.messages = FALSE)
set.seed(123, "L'Ecuyer-CMRG") # for reproducibility
AROC_kernel_men <- AROC.kernel(marker = "bmi",
                               covariate = "age",
                               group = "cvd_idf",
                               tag.h = 0,
                               data = subset(endosyn, gender == "Men"),
                               p = seq(0, 1, l = 101),
                               B = 500,
                               ci.level = 0.95,
                               parallel = "snow", ncpus = 2)

summary(AROC_kernel_men)
```

```
##
## Call:
## AROC.kernel(marker = "bmi", covariate = "age", group = "cvd_idf",
##     tag.h = 0, data = subset(endosyn, gender == "Men"), p = seq(0,
##         1, l = 101), B = 500, ci.level = 0.95, parallel = "snow",
##     ncpus = 2)
##
## Approach: AROC Kernel-based
## ----------------------------------------------
## Area under the covariate-adjusted ROC curve: 0.668 (0.636, 0.708)*
##  * Confidence level:  0.95
##
## Regression function:
##
##                 Group H
## Bandwidth:     5.767820
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Variance function:
##
##                 Group H
## Bandwidth:     6.489771
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Sample sizes:
##                            Group H     Group D
## Number of observations         899         418
## Number of missing data           0           0

# Women
set.seed(123, "L'Ecuyer-CMRG")
AROC_kernel_women <- AROC.kernel(marker = "bmi",
                                 covariate = "age",
                                 group = "cvd_idf",
                                 tag.h = 0,
                                 data = subset(endosyn, gender == "Women"),
                                 p = seq(0, 1, l = 101),
                                 B = 500,
                                 ci.level = 0.95,
                                 parallel = "snow", ncpus = 2)

summary(AROC_kernel_women)

##
## Call:
## AROC.kernel(marker = "bmi", covariate = "age", group = "cvd_idf",
##     tag.h = 0, data = subset(endosyn, gender == "Women"), p = seq(0,
##         1, l = 101), B = 500, ci.level = 0.95, parallel = "snow",
##     ncpus = 2)
##
## Approach: AROC Kernel-based
## ----------------------------------------------
## Area under the covariate-adjusted ROC curve: 0.673 (0.636, 0.716)*
##  * Confidence level:  0.95
##
## Regression function:
##
##                  Group H
## Bandwidth:     3.993242
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Variance function:
##
##                   Group H
## Bandwidth:     18.250812
##
## Kernel Estimator: Local-Constant
## Bandwidth Selection Method: Least Squares Cross-Validation
## Continuous Kernel Type: Second-Order Gaussian
##
## Sample sizes:
##                             Group H     Group D
## Number of observations        1250         273
## Number of missing data           0           0

op <- par(mfcol = c(1,2))
plot(AROC_kernel_women, main = "AROC kernel \n Women", cex.main = 1.5, cex.lab = 1.5,
     cex.axis = 1.5, cex = 1.7)
plot(AROC_kernel_men, main = "AROC kernel \n Men", cex.main = 1.5, cex.lab = 1.5,
     cex.axis = 1.5, cex = 1.7)
par(op)
```



Web Figure 14: Graphical results as provided by the `plot.AROC` function for an object of class `AROC.kernel`. Estimate and 95% pointwise bootstrap confidence interval of the age adjusted ROC curve (AROC) and corresponding AUC. Analyses were done separately for women (left plot) and men (right plot).

Acknowledgements

MX Rodríguez-Álvarez was funded by project MTM2017-82379-R (AEI/FEDER, UE), by the Basque Government through the BERC 2018-2021 program and Elkartek project 3KIA (KK-2020/00049), and by the Spanish Ministry of Science, Innovation, and Universities (BCAM Severo Ochoa accreditation SEV-2017-0718).

References

Dunn, P. K. and Smyth, G. K. (1996). Randomized Quantile Residuals. *Journal of Computational and Graphical Statistics*, 5(3):236–244.

Fan, J. and Gijbels, I. (1996). *Local Polynomial Modelling and Its Applications.* Monographs on Statistics and Applied Probability. Chapman & Hall/CRC.

Faraggi, D. (2003). Adjusting Receiver Operating Characteristic Curves and Related Indices for Covariates. *Journal of the Royal Statistical Society D*, 52(2):179–192.

González-Manteiga, W., Pardo-Fernández, J. C., and van Keilegom, I. (2011). Roc Curves in Non-Parametric Location-Scale Regression Models. *Scandinavian Journal of Statistics*, 38(1):169–184.

Hayfield, T. and Racine, J. S. (2008). Nonparametric Econometrics: The np Package. *Journal of Statistical Software*, 27(5).

Hillis, S. L. and Metz, C. E. (2012). An Analytic Expression for the Binormal Partial Area under the ROC Curve. *Academic Radiology*, 19(12):1491 – 1498.

Hsieh, F. and Turnbull, B. W. (1996). Nonparametric and Semiparametric Estimation of the Receiver Operating Characteristic Curve. *The Annals of Statistics*, 24(1):25–40.

Janes, H. and Pepe, M. S. (2009). Adjusting for Covariate Effects on Classification Accuracy using the Covariate-Adjusted Receiver Operating Characteristic Curve. *Biometrika*, 96(2):371–382.

Pepe, M. S. (1998). Three Approaches to Regression Analysis of Receiver Operating Characteristic Curves for Continuous Test Results. *Biometrics*, 54(1):124–135.

Rodríguez-Álvarez, M. X., Roca-Pardiñas, J., and Cadarso-Suárez, C. (2011). ROC curve and Covariates: Extending Induced Methodology to the Non-Parametric Framework. *Statistics and Computing*, 21(4):483–499.

Silverman, B. W. (1986). *Density Estimation for Statistics and Data Analysis.* Chapman & Hall/CRC.

Wand, M. P. and Jones, M. C. (1994). *Kernel Smoothing.* Chapman & Hall/CRC.

Zou, K. H., Hall, W. J., and Shapiro, D. E. (1997). Smooth Non-Parametric Receiver Operating Characteristic (roc) Curves for Continuous Diagnostic Tests. *Statistics in Medicine*, 16(19):2143–2156.

Zou, K. H., Tempany, C. M., Fielding, J. R., and Silverman, S. G. (1998). Original Smooth Receiver Operating Characteristic Curve Estimation from Continuous Data: Statistical Methods for Analyzing the Predictive Value of Spiral CT of Ureteral Stones. *Academic Radiology*, 5(10):680–687.