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# SMOOTH RISK-BASED PREDICTIVE APPROACHES TO TREATMENT EFFECT HETEROGENEITY: A SIMULATION STUDY

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## Abstract

**Objective:** Compare different risk-based approaches to estimating individualized treatment effects with simulations of the RCT setting. **Study Design and Setting:** We compared different methods for predicting absolute benefit on the basis of an available prognostic index (PI) for risk: A model with the PI and a constant relative treatment effect; models including an interaction of treatment assignment with the PI; 4 quarters of the PI; nonlinear transformations of the PI with increasing flexibility (restricted cubic splines with 3, 4 and 5 knots, respectively); an adaptive method, selecting the optimal model based on Akaike's Information Criterion. Starting from a base case scenario (sample size 4,250, average treatment effect odds ratio 0.8, AUC of the PI 0.75), we considered diverse assumptions of the data generation process of the "true" treatment effect, introducing linear and quadratic interactions of the PI with treatment. We analyzed the effect of varying sample size and discriminative ability of the PI. We evaluated performance using root mean squared error, discrimination for benefit and calibration for benefit. **Results:** The model including a linear interaction of the risk linear predictor with treatment had adequate performance that was robust under the majority of the simulation scenarios. Methods using

restricted cubic splines required larger sample sizes and higher AUC of the PI to achieve adequate performance. The adaptive approach's performance was comparable to the performance of the best model in each scenario. **Conclusion:** In most cases using a model just including a linear interaction of the PI with treatment adequately predicts absolute benefit.

**Keywords** test · test that

## 1 Introduction

Within the setting of patient-centered outcomes research, predictive approaches for assessing heterogeneity of treatment effects (HTE) aim at the development of models predicting either individualized effects or which of two (or more) treatments is better for an individual [1]. In prior work, we divided such methods in three broader categories based on the reference class used for defining patient similarity when making individualized predictions or recommendations [2]. Risk-modeling approaches use prediction of baseline risk as the reference; treatment effect modeling approaches also model treatment-covariate interactions, in addition to risk factors; optimal treatment regime approaches focus on developing treatment assignment rules and therefore rely heavily on modeling treatment effect modifiers.

Risk-modeling approaches to predictive HTE analyses provide a viable option in the absence of well-established treatment effect modifiers [3,4]. In simulations, modeling of effect modifiers in the form of treatment-covariate interactions often led to miscalibrated predictions of benefit, while risk-based methods proved quite robust [5]. Most often, risk-modeling approaches are carried out in two steps: first a risk prediction model is developed externally or internally on the entire RCT population, “blinded” to treatment; then the RCT population is stratified using this prediction model to evaluate risk-based treatment effect variation [6]. However, even though estimates at the risk subgroup level are accurate, this does not apply on the individual level, especially for patients with predicted risk at the boundaries of the risk intervals. Therefore, the risk-stratified approach should be used for exploring and presenting an overview of HTE, while inferences on the individual level should be made with caution.

We aimed to provide an overview of methods that can be used to move from a risk-stratified approach to a continuous one using common smoothing techniques. These methods extend the risk-based framework of predictive HTE analyses to allow predictions on the individual level, within the RCT setting. We carried out a simulation study to compare the performance of these methods under different settings of increasing non-linearity of treatment effects. Finally, we carried out an application on real data as a demonstration of the considered techniques.

## 2 Methods

### 2.1 Simulation scenarios

In the simulated datasets based treatment was allocated at random using a 50/50 split. For each patient we simulated 8 baseline covariates, where  $x_1, \dots, x_4 \sim N(0, 1)$  and  $x_5, \dots, x_8 \sim B(1, 0.2)$ . Outcomes for patients in the control arm were generated from a logistic regression model including all baseline covariates. Coefficient values were such, so that the prediction model had an AUC of 0.75 and an event rate of 20 in the control arm was achieved. Under the base case scenario, outcomes in the treatment arm were created using the same logistic regression model, including a constant treatment odds ratio (OR) of 0.8. The generated samples of the base case scenario were 4,250 (80% power for the detection of an unadjusted OR of 0.8).

We evaluated the effect of sample size considering additional scenarios with sample sizes of 1,064 and 17,000. We also evaluated the effect of prediction performance, adjusting the baseline covariate coefficients, so that AUC values of 0.65 and 0.80 were achieved when validating in a simulated dataset of 500,000 patients.

We simulated binary outcomes in the control arm based on  $\text{expit}(PI)$ , where  $\text{expit}(x) = \frac{e^x}{1+e^x}$ . In the treatment arm outcomes were generated from  $\text{expit}(lp_1)$  with

$$lp_1 = \gamma_2(PI - c)^2 + \gamma_1(PI - c) + \gamma_0,$$

where the coefficients  $\gamma_0, \gamma_1$  and  $\gamma_2$  along with the centering constant  $c$  were set for each simulation scenario. In this way we were able to assess a wide variety of scenarios, ranging from true constant relative treatment effects to moderate and strong linear and quadratic deviations. We also considered scenarios with treatment-covariate interactions. These scenarios include 4 weak interactions ( $OR_{t_x=1}/OR_{t_x=0} = 0.82$ ), 4 strong interactions ( $OR_{t_x=1}/OR_{t_x=0} = 0.61$ ), and 2 weak and 2 strong interactions. Combining all these different settings resulted in a simulation study of 66 scenarios. The exact settings for each scenario are available in the supplementary material.

### 2.2 Individualized risk-based benefit predictions

All methods assume that a risk prediction model is available and can be used to assign individualized predictions. For the simulations we developed the prediction models internally and blinded to treatment using logistic regression including main effects for all baseline covariates and treatment. Predictions on individuals were made setting treatment to 0.

The **stratified HTE method** was suggested as an alternative to traditional subgroup analyses. Patients are stratified into equally-sized risk strata—in this case based on risk quartiles. Absolute effects are estimated using the differences in event rates between treatments within risk quarters. We considered this approach as a reference, expecting it to perform worse than the other candidates, as its objective is not individualized benefit prediction.

We also considered a set of **linear methods**. We fit separate models within treatment arms using only the treatment indicator and the linear predictor of the internal risk prediction model. In the simpler case, we assume a constant relative treatment effect (OR). Absolute benefit is then estimated from  $\text{expit}(lp + \log(\text{OR}))$ , where  $\text{expit}(x) = \frac{e^x}{1+e^x}$  and  $lp$  is the linear predictor of the prediction model. A different approach fits a logistic regression using treatment, risk linear predictor and their interaction. In this case, absolute benefit is estimated from  $\text{expit}(\beta_0 + \beta_{lp}lp) - \text{expit}(\beta_0 + \beta_{t_x} + (\beta_{lp} + \beta_*)lp)$ . We will refer to this method as the linear interaction approach. Finally, we used restricted cubic splines (RCS) to relax the linearity assumption on the effect of the linear predictor [7]. We compared the results for 3, 4 and 5 knots when fitting the splines to introduce increasing flexibility to the methods considered.

### 2.3 Evaluation metrics

Assuming that  $\tau(x) = E\{y \mid x, t_x = 0\} - E\{y \mid x, t_x = 1\}$  is the true benefit for each patient and  $\hat{\tau}(x)$  is the estimated benefit from a method under study, the ideal loss function to use for the considered methods would be the unobservable root mean squared error  $E\{(\hat{\tau} - \tau)^2 \mid x\}$ . However, in simulations the true patient-level benefit is available. Therefore, we estimated RMSE from

$$\text{RMSE} = \frac{1}{n} \sum_{i=1}^n (\tau(x_i) - \hat{\tau}(x_i))^2$$

We also compared the predictive performance of the methods under study. We assessed discrimination using the c-for-benefit statistic described in [8]. Patients in each treatment arm are ranked based on their predicted benefit and then are matched 1:1, dropping patients in the larger treatment arm without a pair. We define *observed* pair-specific treatment benefit as the difference of observed outcomes between the untreated and the treated patient of each pair. Pair-specific *predicted* benefit is defined as the average of predicted benefits within each pair. Then, c-for-benefit is defined as the probability that from two randomly chosen matched patient pairs with unequal observed benefit, the pair with greater observed benefit also has a higher predicted benefit.

We evaluated calibration in a similar manner, using the integrated calibration index (ICI) for benefit [9]. After creating pairs based on predicted benefit, observed benefits are regressed on the predicted benefits using a locally weighted scatterplot smoother (loess). The ICI is the area between the loess fit and the diagonal, with values closer to 0 indicating better calibration.

## 3 Results

### 3.1 Simulations

The model including a constant relative treatment effect had the lowest median RMSE in scenarios where the base case of true constant relative treatment effect ( $\text{OR} = 0.8$ ,  $N = 4,250$  and  $\text{AUC} = 0.75$ ) or moderate relative

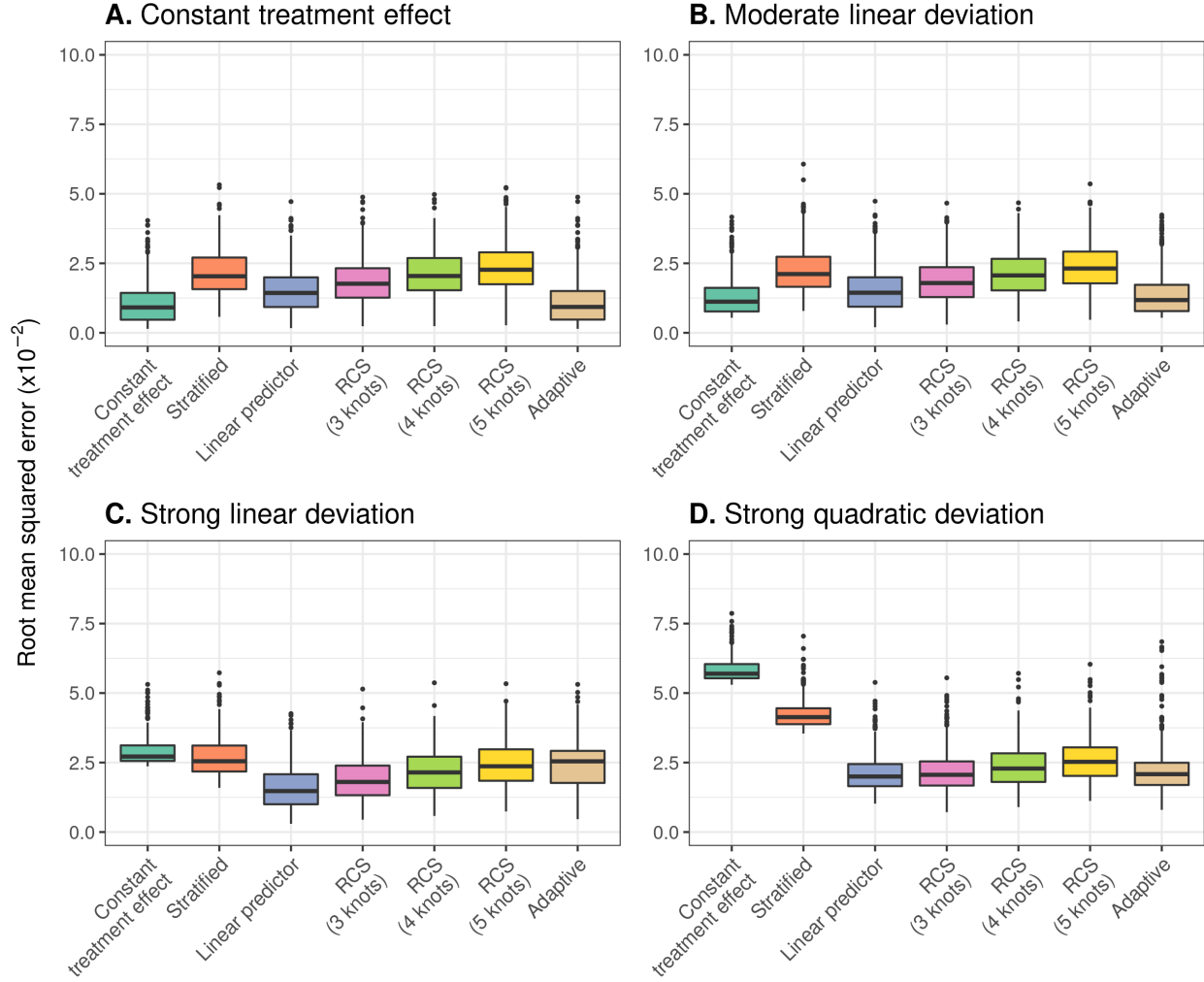


Figure 1: RMSE of the considered methods across 500 replications calculated in a simulated sample of size 500,000. *Panel A* presents the results under the base case scenario of true constant relative treatment effect, with a true prediction AUC of 0.75 and sample size of 4250; *Panel B* presents the results under moderate linear deviations from the base case of constant treatment effects, while holding true prediction AUC and sample size constant; *Panel C* presents the results for strong linear deviations from the base case scenario of constant relative treatment effects; *Panel D* presents the results for strong quadratic deviations from the base case scenario of constant relative treatment effects.

deviations were considered (Figure 1; Panel A). However, when we considered strong linear and quadratic deviations from the base case the linear interaction model performed best (Figure 1; Panels B and C). Only in the case of strong quadratic deviations models including RCS smoothing (3 knots) performed equally well to the linear interaction method. Increasing the number of knots in RCS smoothing resulted in higher error rates across all scenarios. The performance of the adaptive approach was quite comparable with the best performing model in each scenario.

When we increased the sample size ( $N = 17,000$ ), in all scenarios the model more in agreement with the underlying settings had the lowest error rates. Under the base case of constant relative treatment effects ( $OR = 0.8$ ), the

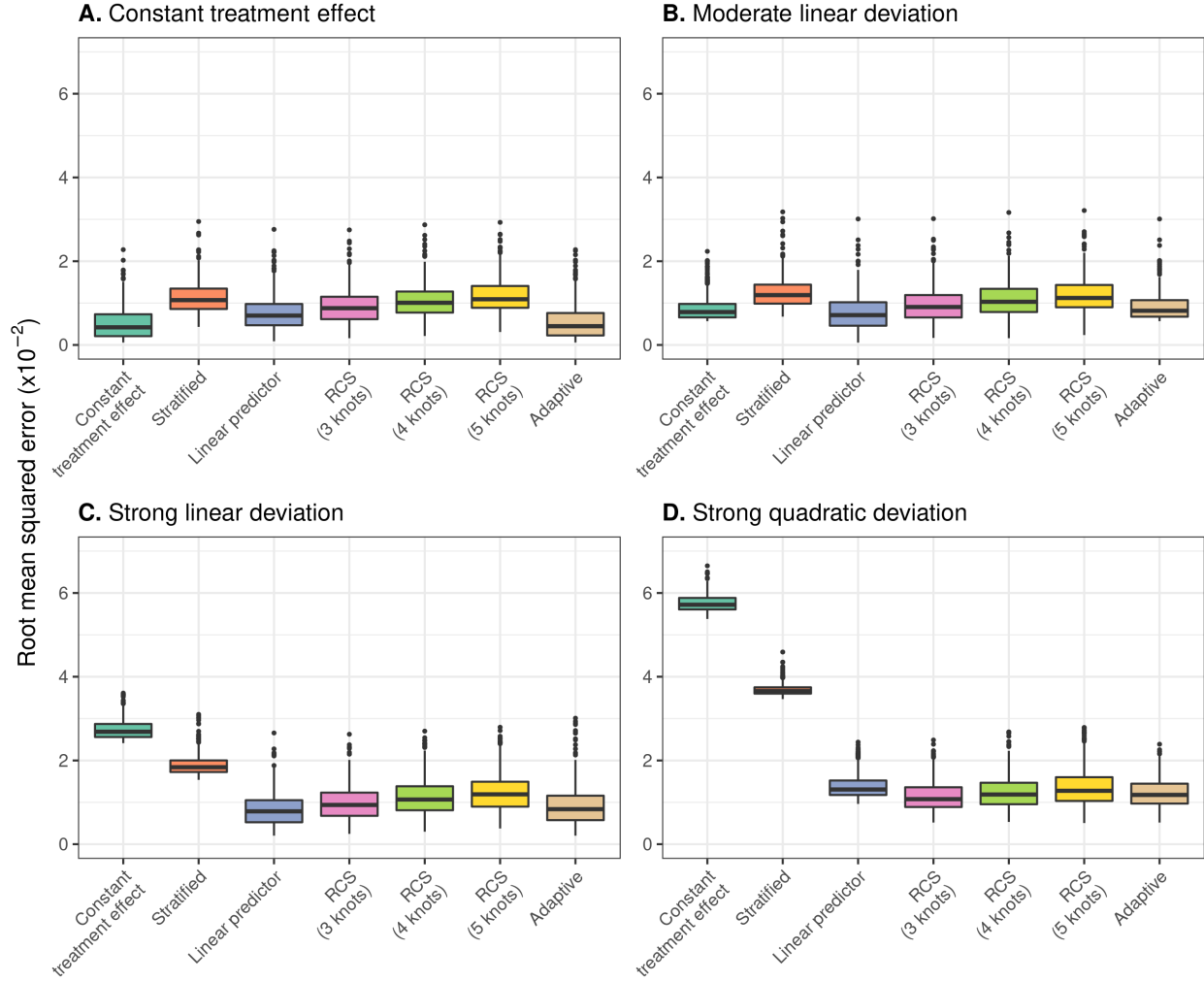


Figure 2: RMSE of the considered methods across 500 replications calculated in a simulated sample of size 500,000. *Panel A* presents the results under the base case scenario of true constant relative treatment effect, with a true prediction AUC of 0.75 and sample size of 17,000; *Panel B* presents the results under moderate linear deviations from the base case of constant treatment effects, while holding true prediction AUC and sample size constant; *Panel C* presents the results for strong linear deviations from the base case scenario of constant relative treatment effects; *Panel D* presents the results for strong quadratic deviations from the base case scenario of constant relative treatment effects.

model including a constant relative treatment effect had the lowest RMSE (Figure 2; Panel A). When introducing moderate and strong linear deviations the linear interaction model performed best (Figure 2; Panels B and C). In the case of true strong quadratic deviations from the base case of constant relative effects, the more flexible RCS smoothing models (3 knots) had the lowest RMSE. Again, the increased flexibility of RCS smoothing with higher number of knots resulted in overfitting and worse performance (Figure 2; Panel D).

When we increased the true prediction AUC to 0.85, models including RCS smoothing had the lowest RMSE in the presence of strong quadratic deviations from the base case of true constant relative treatment effects (Figure 3; Panel D). However, with milder deviations, the linear interaction model had the lowest RMSE with the RCS

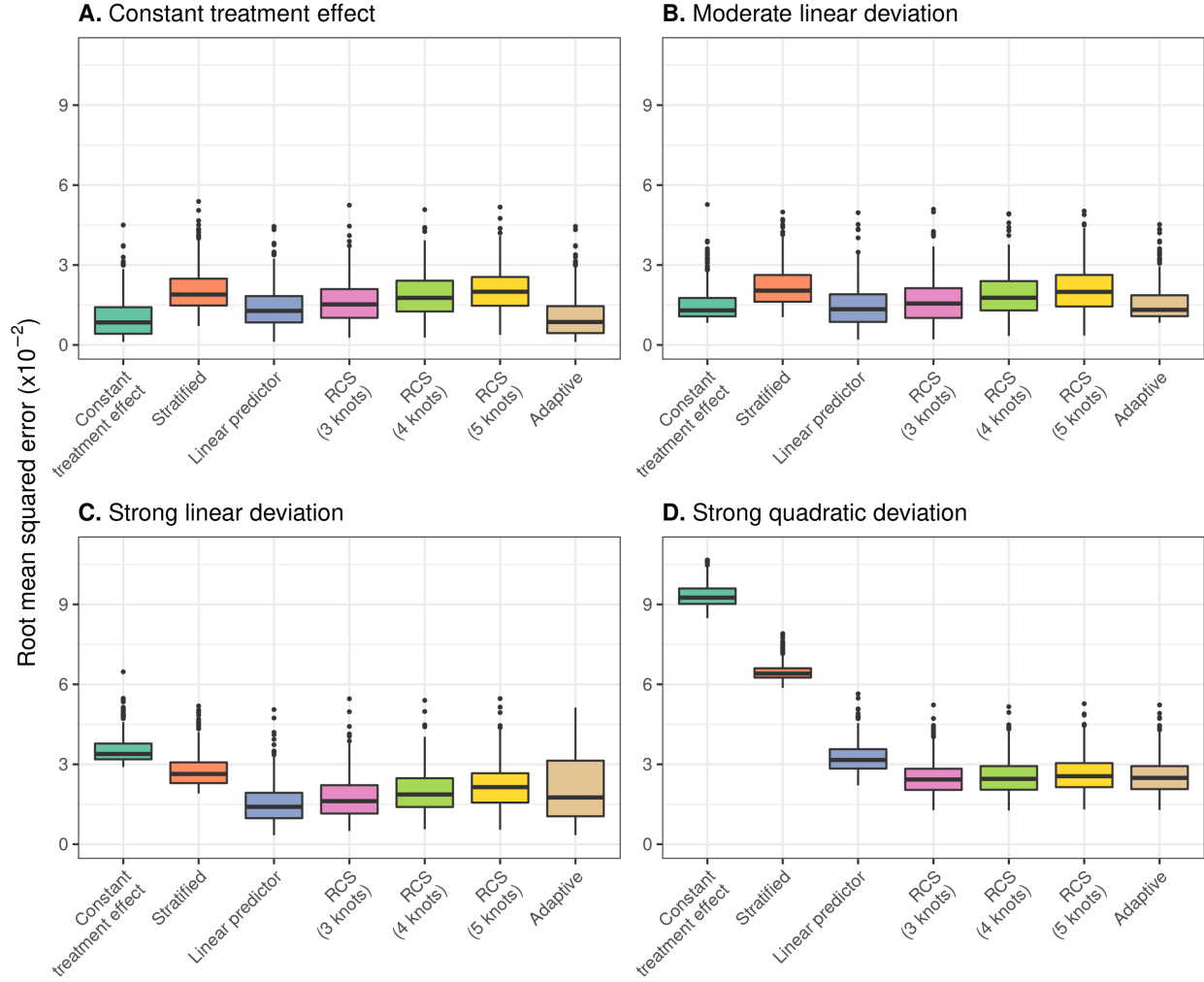


Figure 3: RMSE of the considered methods across 500 replications calculated in a simulated sample of size 500,000. *Panel A* presents the results under the base case scenario of true constant relative treatment effect, with a true prediction AUC of 0.85 and sample size of 4,250; *Panel B* presents the results under moderate linear deviations from the base case of constant treatment effects, while holding true prediction AUC and sample size constant; *Panel C* presents the results for strong linear deviations from the base case scenario of constant relative treatment effects; *Panel D* presents the results for strong quadratic deviations from the base case scenario of constant relative treatment effects.

smoothing methods (3 knots) being a close second (Figure 3; Panels B and C). Increasing the number of knots of  
RCS smoothing resulted in increased RMSE, which was less pronounced in the case of strong quadratic deviations.  
All candidate methods demonstrated comparable discrimination for benefit in all scenarios where linear and  
quadratic deviations from the base case of constant treatment effect were considered (N=4,250; AUC = 0.75).  
However, models including a linear interaction with the risk linear predictor tended to present much lower variability  
compared to all other model-based and smoothing approaches (Figure 4). We also observed an increasing trend of  
discrimination for benefit variability with increasing number of restricted cubic spline knots in all scenarios.

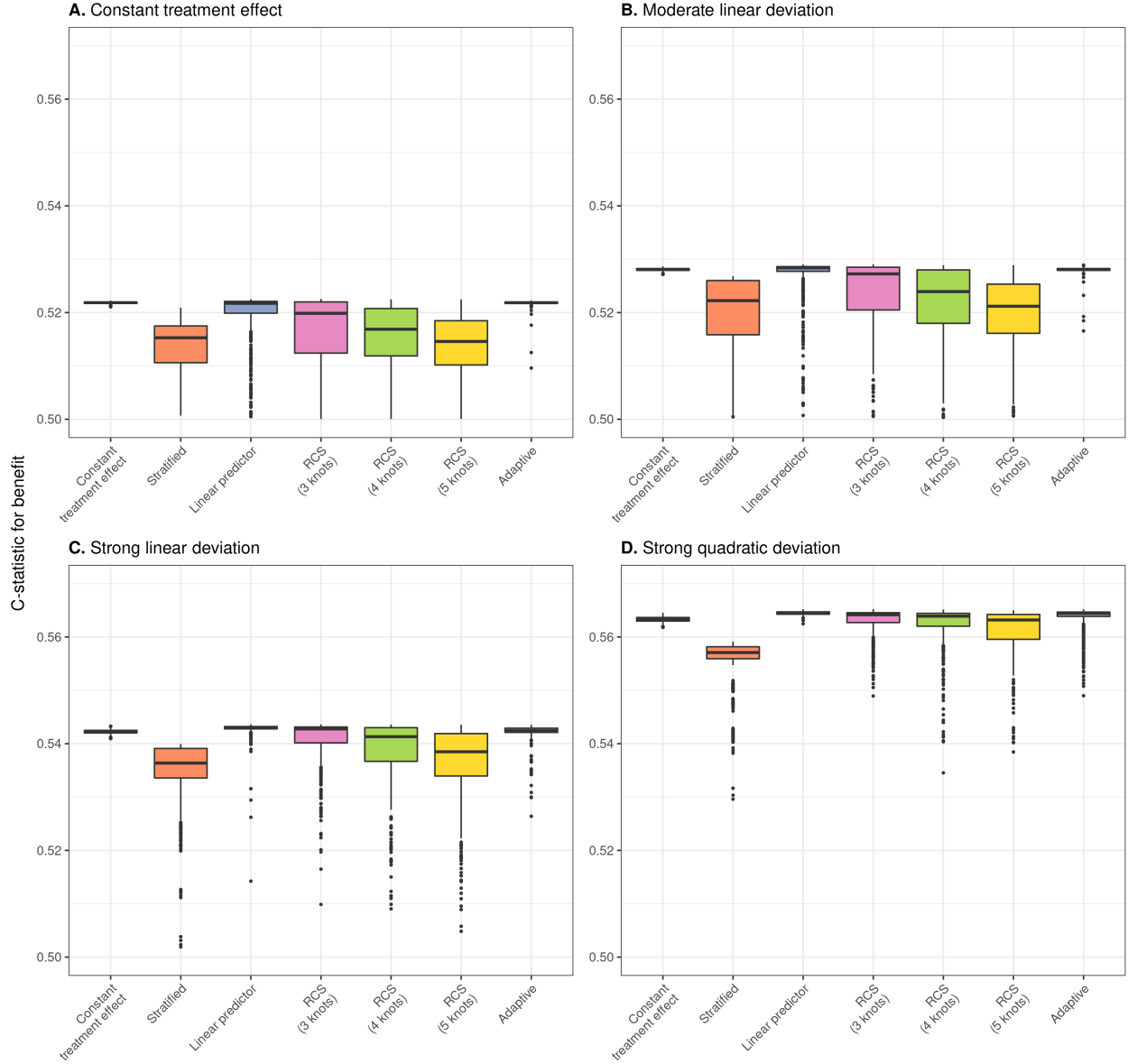


Figure 4: Discrimination for benefit of the considered methods across 500 replications calculated in a simulated sample of size 500,000. *Panel A* presents the results under the base case scenario of true constant relative treatment effect, with a true prediction AUC of 0.75 and sample size of 4250; *Panel B* presents the results under moderate linear deviations from the base case of constant treatment effects, while holding true prediction AUC and sample size constant; *Panel C* presents the results for strong linear deviations from the base case scenario of constant relative treatment effects; *Panel D* presents the results for strong quadratic deviations from the base case scenario of constant relative treatment effects.



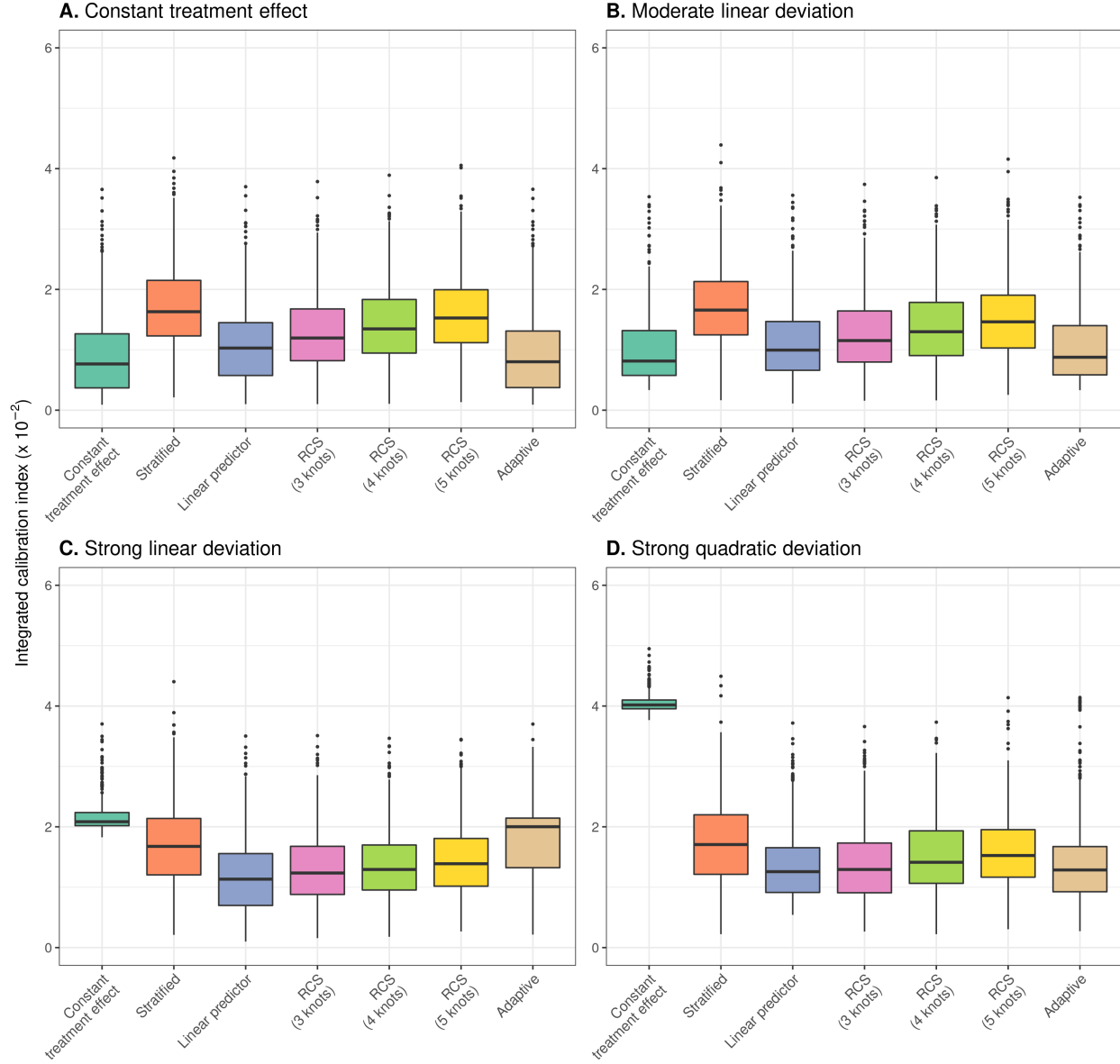


Figure 5: Calibration for benefit of the considered methods across 500 replications calculated in a simulated sample of size 500,000. *Panel A* presents the results under the base case scenario of true constant relative treatment effect, with a true prediction AUC of 0.75 and sample size of 4250; *Panel B* presents the results under moderate linear deviations from the base case of constant treatment effects, while holding true prediction AUC and sample size constant; *Panel C* presents the results for strong linear deviations from the base case scenario of constant relative treatment effects; *Panel D* presents the results for strong quadratic deviations from the base case scenario of constant relative treatment effects.

When focusing on calibration, the linear interaction model had the lowest median ICI for benefit in the majority of scenarios except for the scenarios where moderate linear deviations from the base case were considered. In that case constant treatment effect models demonstrated the best performance, very comparable to the linear interaction model's performance, nonetheless (Figure 5; Panels A, B, and C).

## 3.2 Real data

We demonstrate the different methods for individualizing treatment benefits using data from 30,510 patients with an acute myocardial infarction (MI) included in the GUSTO-I trial. 10,348 patients were randomized to tissue plasminogen activator (tPA) treatment and 20,162 were randomized to streptokinase. The outcome of interest was 30-day mortality, recorded for all patients.

In line with previous analyses [10,11], we fitted a logistic regression model with 6 baseline covariates, i.e. age, Killip class, systolic blood pressure, heart rate, an indicator of previous MI, and the location of MI, to predict 30-day mortality risk. A constant effect of treatment was included in the model. When deriving risk predictions for individuals we set the treatment indicator to 0. More information on model development can be found in the supplement.

We used the risk linear predictor to fit the the proposed methods under study for individualizing absolute benefit predictions. All methods had quite comparable results, in the sense that we predicted increasing benefits for patients with higher baseline risk predictions. In terms of c-for-benefit (validated internally) all models had quite comparable performance ranging from 0.519 (RCS smoothing with 3 knots) to 0.542 (RCS smoothing with 4 knots). Similar conclusions could be drawn in terms of ICI-for-benefit which ranged from 0.0039 (linear interaction approach) to 0.0053 (RCS smoothing with 4 knots).

The adaptive approach picked the model with RCS smoothing with 4 knots, which had quite comparable performance to the smooth fit with 5 knots. However, for lower baseline risk these 2 models predicted implausible benefits and maybe should be avoided when applying such models in practice. The linear interaction model and the model with RCS smoothing (3 knots) made very similar predictions and also followed quite closely the evolution of the stratified estimates. In this case, we observed that even using a simple model with a constant relative treatment effect can result in very similar benefit predictions as other more complex approaches.

## 4 Discussion

We have carried out a simulation study comparing different approaches for individualized benefit prediction using baseline risk as the reference. These methods included a constant treatment effect model, a model including a simple linear interaction of the risk linear predictor with treatment, and models using smoothing with restricted cubic splines with 3, 4, and 5 knots. Performance was assessed evaluating error rates using RMSE and benefit prediction performance using some novel methods for evaluating discrimination and calibration for benefit.

The linear interaction model proved to be flexible enough to adequately predict benefit under a wide range of scenarios. It had lower error rates and usually the highest c-for-benefit with the lower variability across simulation replications. Its benefit predictions were also well-calibrated across the majority of the simulation settings. Models with RCS smoothing with 3 knots performed very similarly, only outperforming the linear interaction model in the

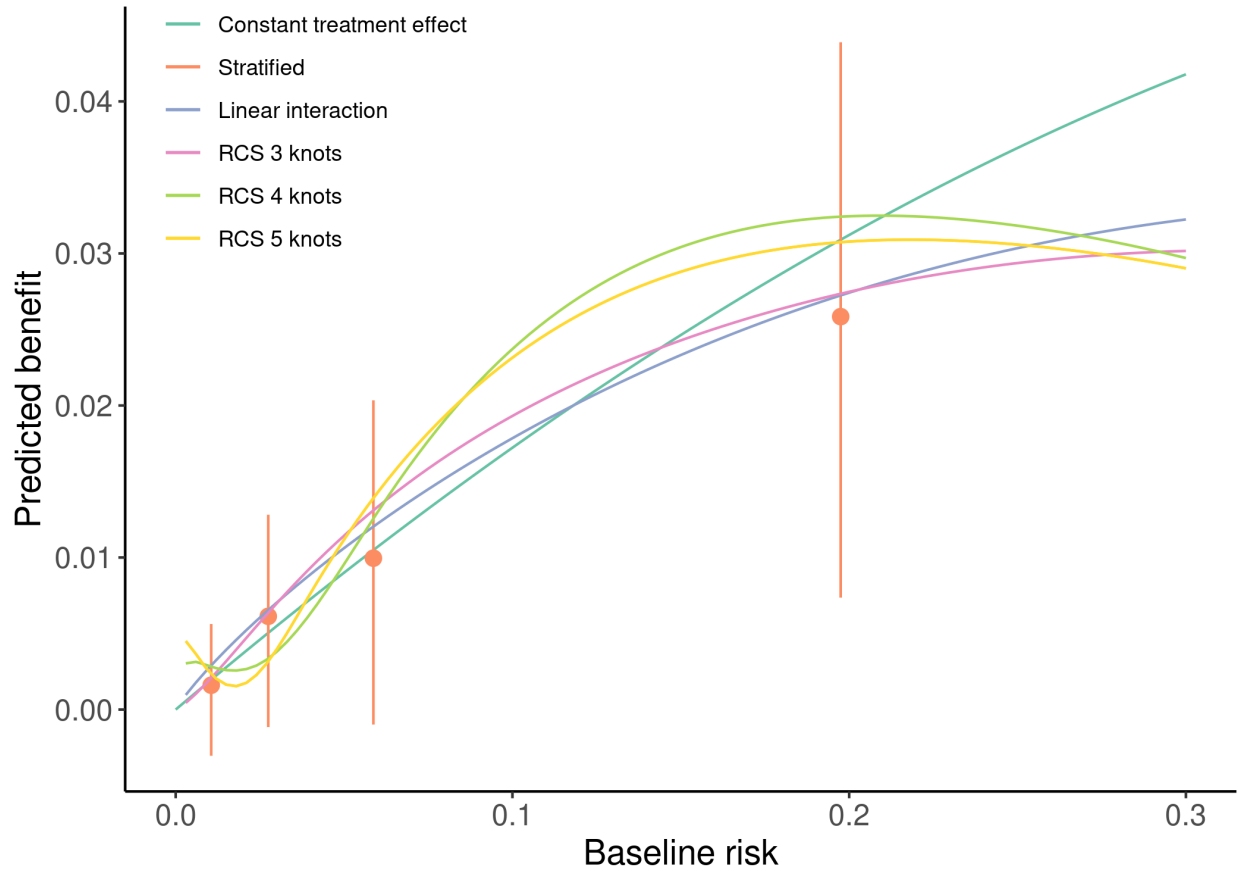


Figure 6: Individualized absolute benefit predictions based on baseline risk when using a constant treatment effect approach, a linear interaction approach and RCS smoothing using 3, 4 and 5 knots. Risk stratified estimates of absolute benefit are presented within quartiles of baseline risk as reference.

presence of strong quadratic deviations from the base case scenario of constant relative treatment effects. These simpler methods proved to have quite robust performance across all scenarios, which was not the case for more flexible approaches.

Methods with RCS smoothing with 4 or 5 knots proved to be data-hungry and this often led to overfitting with smaller sample sizes. This resulted in higher RMSE, increased variability of discrimination for benefit and worse-calibrated benefit predictions across simulation replications. Even with larger sample sizes and strong quadratic deviations from the base case scenario of constant relative treatment effects, these more flexible RCS smoothing methods did not outperform simpler RCS smoothing with 3 knots. More flexible approaches usually do not come with any added value, unless we expect extreme heterogeneity in treatment effects.

The constant treatment effect model, despite having adequate performance even in the presence of weak treatment effect heterogeneity on the relative scale, it quickly broke down with stronger deviations from the base case scenario of constant effects. In these cases, the stratified approach generally had lower error rates compared to the constant treatment effect model. In concept, the stratified approach lies between the constant effects model and

154 smoother approaches, only assuming constant treatment effects within strata of predicted risk and, therefore, is  
155 more sensitive to treatment effect heterogeneity. However, these stepwise benefit estimates can only be used as  
156 a demonstration of treatment effect heterogeneity, identifying patient subgroups where treatment benefits are  
157 expected to be higher or lower, and should not be used to make individualized absolute benefit predictions.

158 Increasing the true prediction AUC by increasing the predictor coefficients of the true risk model reduced RMSE  
159 for all methods, similar to increasing the sample size. Higher AUC translates in higher variability of predicted  
160 risks, which, in turn, allows the considered methods to better follow the evolution of treatment benefit. Higher  
161 prediction AUC also led to higher absolute values of c-for-benefit. Even though, model performance appears to be  
162 very important for the performance of these methods, prediction model development was outside the scope of this  
163 work and has already been studied quite extensively [5,12,13].

164 Risk-based approaches to predictive HTE assume that benefit is a function of baseline risk. A limitation of our  
165 study is that this was assumed to be the case in the majority of the simulation scenarios. Even though our main  
166 conclusions did not change when simulating true treatment-covariate interactions (results in supplement), RMSE  
167 had higher values. The linear interaction model under these scenarios again had the best overall performance under  
168 different sizes of the interaction effects. This can be explained by the fact that linear interactions with treatment  
169 were simulated, thus favoring the linear interaction model. In studies evaluating prediction model development,  
170 the underlying outcome generation process sometimes proved to affect performance of certain methods [14]. This  
171 might be the case here as well and should be explored in more extensive future simulation studies.

172 Recent years have seen an increased interest in predictive HTE approaches focusing on individualized benefit  
173 predictions. In our simulations we only focused on risk-based methods, using baseline risk as a reference in a  
174 two-stage approach to individualizing benefit predictions. However, there is a plethora of different methods, ranging  
175 from treatment effect modeling to tree-based approaches available in more recent literature [15–17]. Simulations  
176 are also needed to assess relative performance and define the settings where these break down or outperform each  
177 other.

178 In conclusion, we carried out a simulation study comparing different risk-based approaches to individualizing benefit  
179 predictions. Simpler models including a linear interaction with the risk linear predictor or RCS smoothing with 3  
180 knots had adequate performance under a wide range scenarios. An adaptive approach based on selecting among  
181 the considered methods using AIC had satisfactory performance.

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