

# Linear interaction of treatment with baseline risk was sufficient for predicting individualized benefit

Alexandros Rekkas<sup>a</sup>, Peter R. Rijnbeek<sup>a</sup>, Ewout W. Steyerberg<sup>b</sup>, David van Klaveren<sup>c</sup>

<sup>a</sup>*Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands*

<sup>b</sup>*Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands*

<sup>c</sup>*Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands*

---

## Abstract

**Objective:** To compare different risk-based methods predicting individualized treatment effects in RCTs.

**Study Design and Setting:** We simulated RCT data using diverse assumptions for the average treatment effect, a

baseline prognostic index of risk (PI), the shape of its interaction with treatment (none, linear, quadratic or non-monotonic) and the magnitude of treatment-related harms. In each sample we predicted absolute benefit using: models with a constant relative treatment effect; stratification in quarters of the PI; models including a linear interaction of treatment with the PI; models including an interaction of treatment with a restricted cubic spline (RCS) transformation of the PI; an adaptive approach using Akaike's Information Criterion. We evaluated predictive performance using root mean squared error and measures of discrimination and calibration for benefit.

**Results:** The linear-interaction model and the RCS-interaction model outperformed the constant treatment effect model in many simulation scenarios. The RCS-model was optimal when quadratic or non-monotonic deviations from a constant treatment effect were stronger, and when sample size was larger. Larger sample size also supported the adaptive approach. **Conclusion:** An interaction between risk and treatment assignment generally improved treatment effect predictions. Non-linear RCS interactions should be considered for larger sample size.

**Keywords:** treatment effect heterogeneity absolute benefit prediction models

---

## <sup>1</sup> 1. Introduction

<sup>2</sup> Predictive approaches for assessing heterogeneity of treatment effects (HTE) aim at the development of models  
<sup>3</sup> predicting either individualized effects or which of two (or more) treatments is better for an individual [1]. In prior  
<sup>4</sup> work, we divided such methods in three broader categories based on the reference class used for defining patient  
<sup>5</sup> similarity when making individualized predictions or recommendations [2]. Risk-modeling approaches use prediction  
<sup>6</sup> of baseline risk as the reference; treatment effect modeling approaches also model treatment-covariate interactions,  
<sup>7</sup> in addition to risk factors; optimal treatment regime approaches focus on developing treatment assignment rules  
<sup>8</sup> and therefore rely heavily on modeling treatment effect modifiers.

<sup>9</sup> Risk-modeling approaches to predictive HTE analyses provide a viable option in the absence of well-established

10 treatment effect modifiers [3,4]. In simulations, modeling of effect modifiers, i.e. treatment-covariate interactions,  
11 often led to miscalibrated predictions of benefit, while risk-based methods proved quite robust [5]. Most often,  
12 risk-modeling approaches are carried out in two steps: first a risk prediction model is developed externally or  
13 internally on the entire RCT population, “blinded” to treatment; then the RCT population is stratified using this  
14 prediction model to evaluate risk-based treatment effect variation [6]. This two-step approach identified substantial  
15 absolute treatment effect differences between low-risk and high-risk patients in a re-analysis of 32 large trials  
16 [7]. However, even though estimates at the risk subgroup level may be accurate, these estimates do not apply  
17 to individual patients, especially for patients with predicted risk at the boundaries of the risk intervals. Hence,  
18 the risk-stratified approach is useful for exploring and presenting HTE, but is not useful for supporting treatment  
19 decisions for individual patients.

20 To individualize treatment effects, the recent PATH statement suggested various risk-based models including  
21 a prognostic index of baseline risk (PI) and treatment assignment [3,4]. We aimed to summarize and compare  
22 different risk-based models for predicting individualized treatment effects. We simulated RCT settings to compare  
23 the performance of these models under different assumptions of the relationship between baseline risk and treatment.  
24 We illustrated the different models by a case study of predicting individualized effects of tissue plasminogen  
25 activator (tPA) versus streptokinase treatment in patients with an acute myocardial infarction (MI).

## 26 **2. Methods**

### 27 *2.1. Simulation scenarios*

28 We simulated a typical RCT that is undertaken to compare a binary outcome (e.g. death) between a group  
29 of treated patients in the treatment arm and a group of untreated patients in the control arm. For each patient  
30 we generated 8 baseline covariates  $x_1, \dots, x_4 \sim N(0, 1)$  and  $x_5, \dots, x_8 \sim B(1, 0.2)$ . Treatment was allocated  
31 using a 50:50 split. Outcomes for patients in the control arm were generated from a logistic regression model  
32 including all baseline covariates. In the base scenarios coefficient values were such, that the AUC of the logistic  
33 regression model was 0.75 and the event rate in the control arm was 20%. Binary outcomes in the control arm  
34 were generated from Bernoulli variables with true probabilities  $P(y = 1|X, t_x = 0) = \text{expit}(PI) = \frac{e^{PI}}{1+e^{PI}}$ .

Outcomes in the treatment arm were generated using 3 base scenarios: absent treatment effect ( $OR = 1$ ),  
moderate treatment effect ( $OR = 0.8$ ) and strong treatment effect ( $OR = 0.5$ ). We started with simulating  
outcomes based on true constant relative treatment effects for the 3 base scenarios. We then simulated linear,  
quadratic and non-monotonic deviations from constant treatment effects using:

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

35 where  $lp_1$  is the true linear predictor in the treatment arm, so that  $P(y = 1|X, t_x = 1) = \text{expit}(lp_1)$ . Finally, we  
36 simulated scenarios where a constant absolute harm is applied across all treated patients. In this case we have  
37  $P(y = 1|X, t_x = 1) = \text{expit}(lp_1) + \text{harm}$ .

38 The sample size for the base scenarios was set to 4,250 (80% power for the detection of a marginal OR of 0.8).  
39 We evaluated the effect of smaller or larger sample sizes of 1,063 (4,250 divided by 4) and 17,000 (4250 multiplied  
40 by 4), respectively. We also evaluated the effect of worse or better discriminative ability for risk, adjusting the  
41 baseline covariate coefficients, such that the AUC of the regression model in the control arm was 0.65 and 0.85  
42 respectively.

43 Combining all these settings resulted in a simulation study of 648 scenarios (exact settings in the supplementary  
44 material). With these scenarios we were able to cover the observed treatment effect heterogeneity in 32 large trials  
45 as well as many other potential variations of risk-based treatment effect [7].

46 *2.2. Individualized risk-based benefit predictions*

47 All risk-based methods assume that a risk prediction model is available to assign risk predictions to individual  
48 patients. For the simulations we developed a prediction model internally, using logistic regression including main  
49 effects for all baseline covariates and treatment assignment. Risk predictions for individual patients were based on  
50 treatment assignment to the control arm, that is setting treatment assignment to 0.

51 A *stratified HTE method* has been suggested as an alternative to traditional subgroup analyses. Patients are  
52 stratified into equally-sized risk strata—in this case based on risk quartiles. Absolute treatment effects within risk  
53 strata are estimated by the difference in event rate between patients in the control arm and patients in the treated  
54 arm. We considered this approach as a reference, expecting it to perform worse than the other candidates, as its  
55 objective is not to individualize benefit prediction.

56 Second, we considered a model which assumes *constant relative treatment effect* (constant odds ratio). Hence,  
57 absolute benefit is predicted from  $\hat{\tau}(\mathbf{x}) = \text{expit}(PI + \log(OR))$ .

58 Third, we considered a logistic regression model including treatment, the prognostic index, and their linear  
59 interaction. Absolute benefit is then estimated from  $\hat{\tau}(\mathbf{x}) = \text{expit}(\beta_0 + \beta_{PI}PI) - \text{expit}(\beta_0 + \beta_{t_x} + (\beta_{PI} + \beta_*)PI)$ .  
60 We will refer to this method as the *linear interaction* approach.

61 Fourth, we used *restricted cubic splines* (RCS) to relax the linearity assumption on the effect of the linear  
62 predictor [8]. We considered splines with 3 (RCS-3), 4 (RCS-4) and 5 (RCS-5) knots to compare models with  
63 different levels of flexibility.

64 Finally, we considered an adaptive approach using Akaike's Information Criterion (AIC) for model selection.  
65 The candidate models were: a constant treatment effect model, a model with a linear interaction with treatment  
66 and RCS models with 3, 4 and 5 knots.

67 **2.3. Evaluation metrics**

68 We evaluated the predictive accuracy of the considered methods by the root mean squared error (RMSE):

$$\text{RMSE} = \sqrt{\frac{1}{n} \sum_{i=1}^n (\tau(\mathbf{x}_i) - \hat{\tau}(\mathbf{x}_i))^2}$$

69 We compared the discriminative ability of the methods under study using c-for-benefit [9]. The c-for-benefit  
70 represents the probability that from two randomly chosen matched patient pairs with unequal observed benefit,  
71 the pair with greater observed benefit also has a higher predicted benefit. To be able to calculate observed benefit,  
72 patients in each treatment arm are ranked based on their predicted benefit and then matched 1:1 across treatment  
73 arms. *Observed* treatment benefit is defined as the difference of observed outcomes between the untreated and  
74 the treated patient of each matched patient pair. *Predicted* benefit is defined as the average of predicted benefit  
75 within each matched patient pair.

76 We evaluated calibration in a similar manner, using the integrated calibration index (ICI) for benefit [10]. The  
77 observed benefits are regressed on the predicted benefits using a locally weighted scatterplot smoother (loess).  
78 The ICI-for-benefit is the average absolute difference between predicted and smooth observed benefit. Values  
79 closer to 0 represent better calibration.

80 **3. Results**

81 **3.1. Simulations**

82 The linear interaction model outperformed all RCS methods in terms of RMSE in scenarios with true constant  
83 relative treatment effect ( $\text{OR} = 0.8$ ,  $N = 4,250$  and  $\text{AUC} = 0.75$ ), strong linear and even strong quadratic deviations  
84 from a constant relative treatment effect (Figure 1; panels A-C). However, with non-monotonic deviations from a  
85 constant relative treatment effect, the RMSE of the linear interaction model increased substantially, especially in the  
86 presence of treatment-related harms (Figure 1; panel D). In these scenarios, RCS-3 outperformed all other methods  
87 in terms of RMSE. The constant treatment effect approach had overall best performance under true constant  
88 treatment effect settings, but was sensitive to all considered deviations, resulting in increased RMSE. Finally,  
89 the adaptive approach had comparable performance to the best-performing method in each scenario. However,  
90 in comparison with the best-performing approach, its RMSE was more variable across the 1000 replications  
91 in the scenarios with linear and non-monotonic deviations, especially when also including moderate or strong  
92 treatment-related harms. This is caused by wrongly selecting the constant treatment effect model in a substantial  
93 proportion of the replications (Supplement, Table XX).

94 In the scenario with a true constant relative treatment effects, the adaptive approach selected the constant  
95 effect model for the majority of the replications, even in the presence of treatment-related harms (96% of the

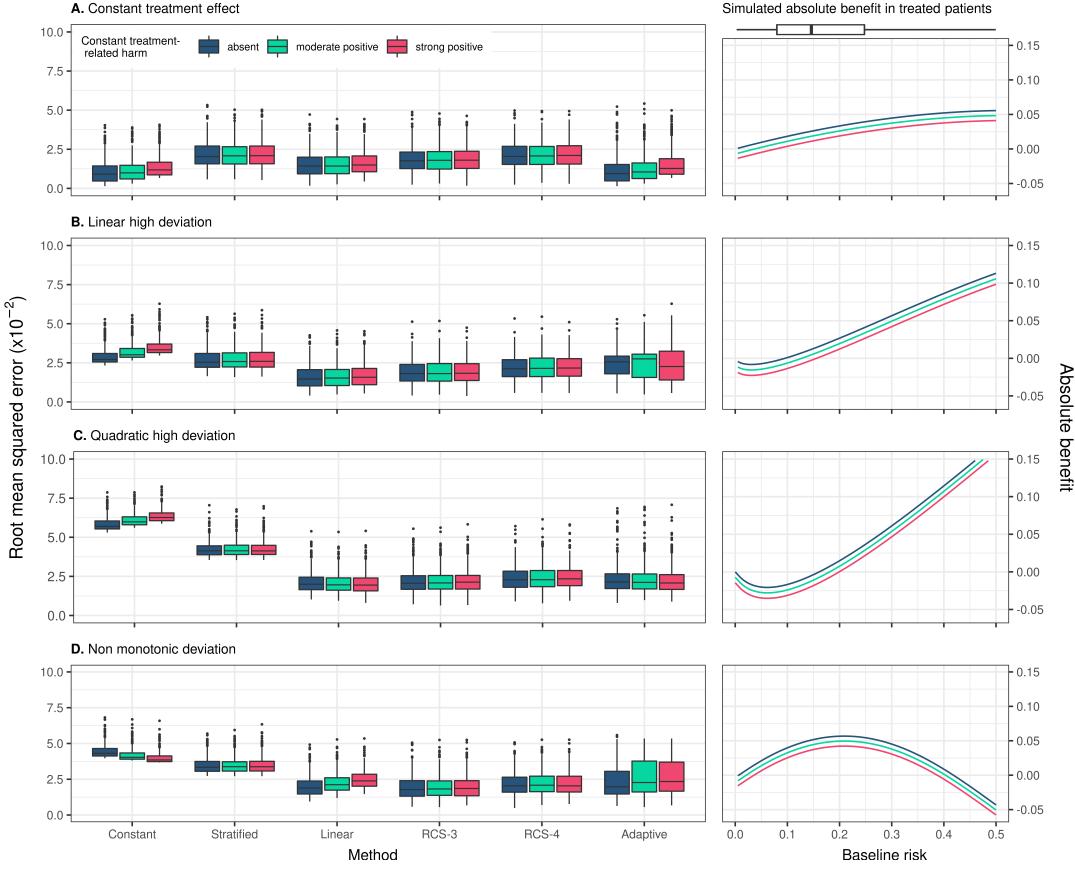


Figure 1: RMSE of the considered methods across 500 replications calculated in a simulated super-population of size 500,000. The scenario with true constant relative treatment effect (panel A) had a true prediction AUC of 0.75 and sample size of 4250. The RMSE is also presented for strong linear (panel B), strong quadratic (panel C), and non-monotonic (panel D) from constant relative treatment effects. Panels on the right side present the true relationship between baseline risk (x-axis) and absolute treatment benefit (y-axis). The 2.5, 25, 50, 75, and 97.5 percentiles of the risk distribution are expressed by the boxplot.

replications without harms and 88% with strong harms). With strong linear or quadratic deviations and increasing treatment-related harms the adaptive approach increasingly favored the linear interaction model. With non-monotonic deviations, we observed increasing selection frequencies for RCS-3 with increasing treatment harms (from 32% with no harms to 53% with strong harms), whereas selection frequencies for the linear interaction model dropped from 40% with no harms to 7% with strong harms. Finally, in the case of strong linear and non-monotonic deviations selection frequencies of the constant treatment effect model remained high despite increasing treatment harms (Supplement, Table XX).

Increasing the sample size to 17,000 favored RCS-3 the most, as it achieved lowest or close to lowest RMSE across all scenarios (Figure 2). Especially in cases of strong quadratic and non-monotonic deviations RCS-3 had lower RMSE (median 0.011 for strong quadratic deviations and 0.010 for non-monotonic deviations with no treatment-related harms) compared to the linear interaction approach (median 0.013 and 0.014, respectively), regardless of the strength of treatment-related harms. Due to the large sample size, the RMSE of the adaptive

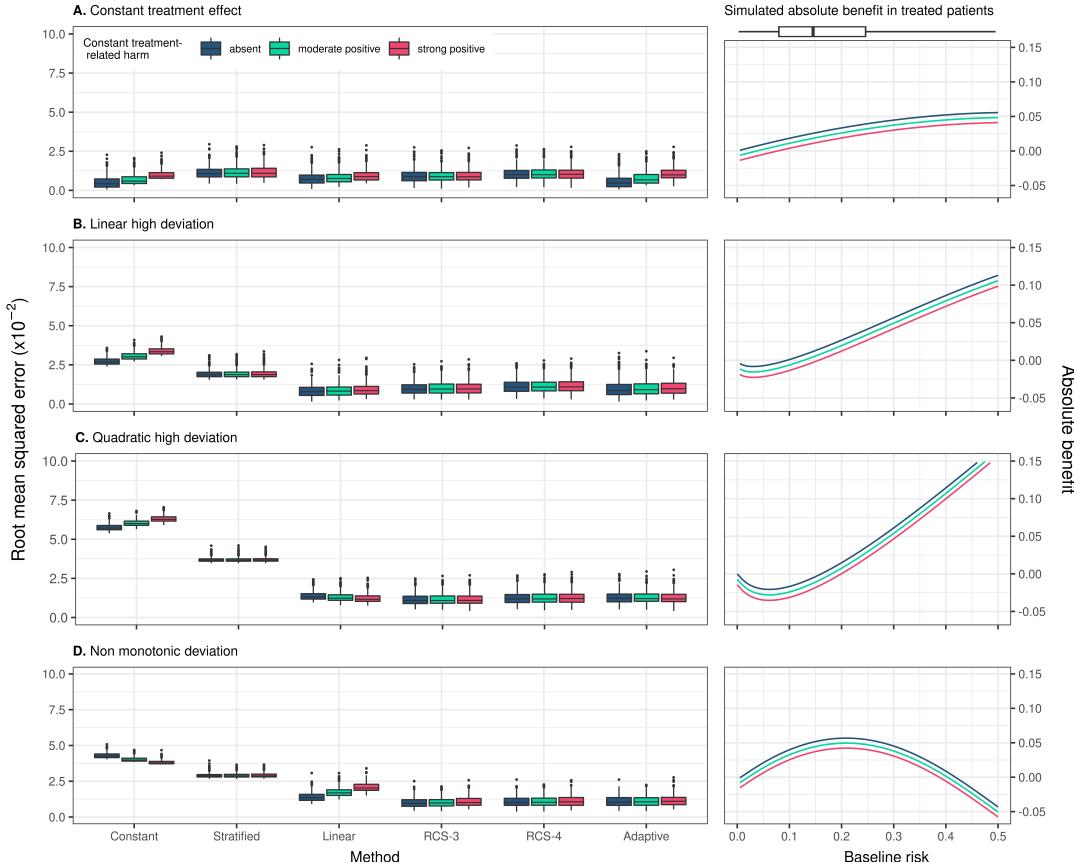


Figure 2: RMSE of the considered methods across 500 replications calculated in a simulated sample of size 500,000. Sample size 17,000 rather than 4250 in Figure 1

108 approach was even more similar to the best-performing method, and the constant relative treatment effect model  
 109 was less often wrongly selected (**numbers????**).

110 When we increased the AUC of the true prediction model to 0.85 (OR = 0.8 and N = 4,250). RCS-3 had the  
 111 lowest RMSE in the case of strong quadratic or non-monotonic deviations and very comparable performance to  
 112 the – optimal – linear interaction model in the case of strong linear deviations (median RMSE 0.016 for RCS-3  
 113 compared to 0.014 for the linear interaction model). As observed in the base case scenario the adaptive approach  
 114 wrongly selected the constant treatment effect model (23% and 25% of the replications in the strong linear and  
 115 non-monotonic deviation scenarios without treatment-related harms, respectively), leading to more variability of  
 116 the RMSE.

117 In comparison with the true approach, dsicrimination for benefit in the scenario with a constant relative  
 118 treatment effect was only slightly lower for the linear interaction model, but more substantially lower for the  
 119 non-linear RCS approaches (Figure 4; panel A). With strong linear or quadratic deviations from a constant  
 120 relative treatment effect, all methods discriminated quite similarly (Figure 4; panels B-C). In the scenario with  
 121 non-monotonic deviations, the constant effect model had much lower discriminative ability compared to non-linear

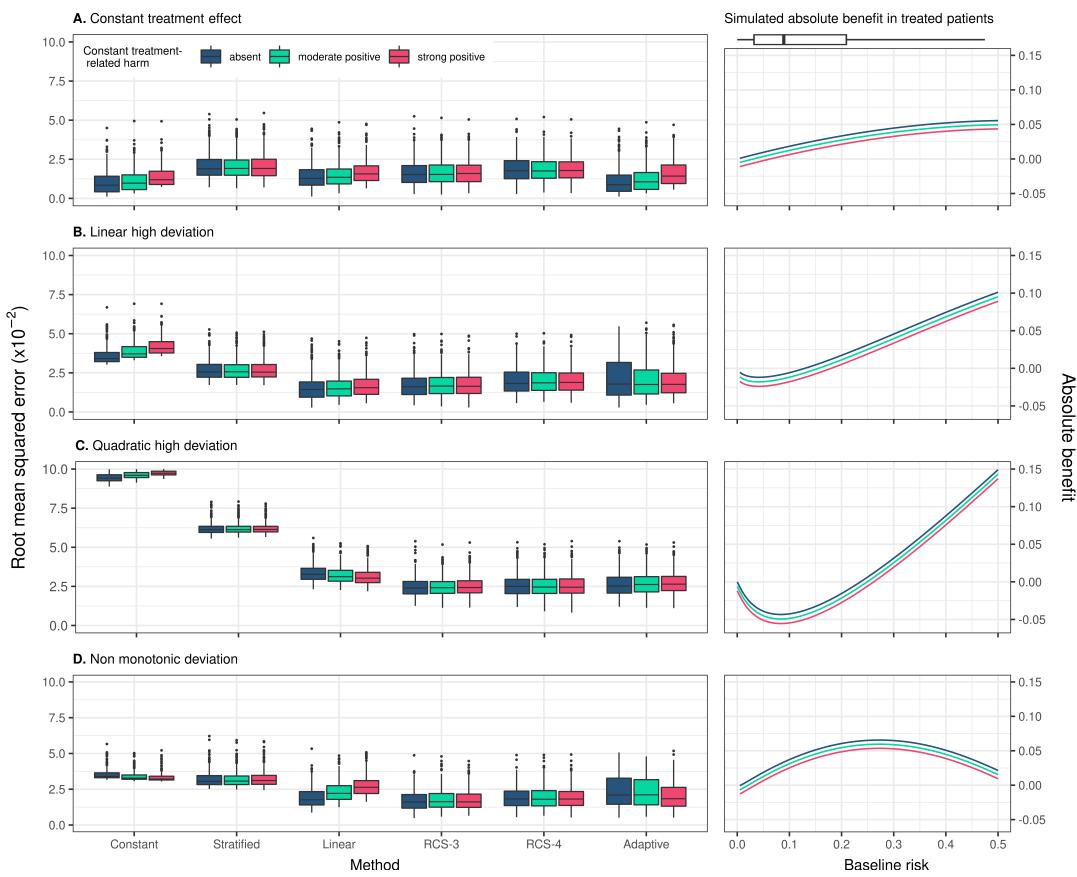


Figure 3: RMSE of the considered methods across 500 replications calculated in a simulated sample of size 500,000. True prediction AUC of 0.85 and sample size of 4,250.

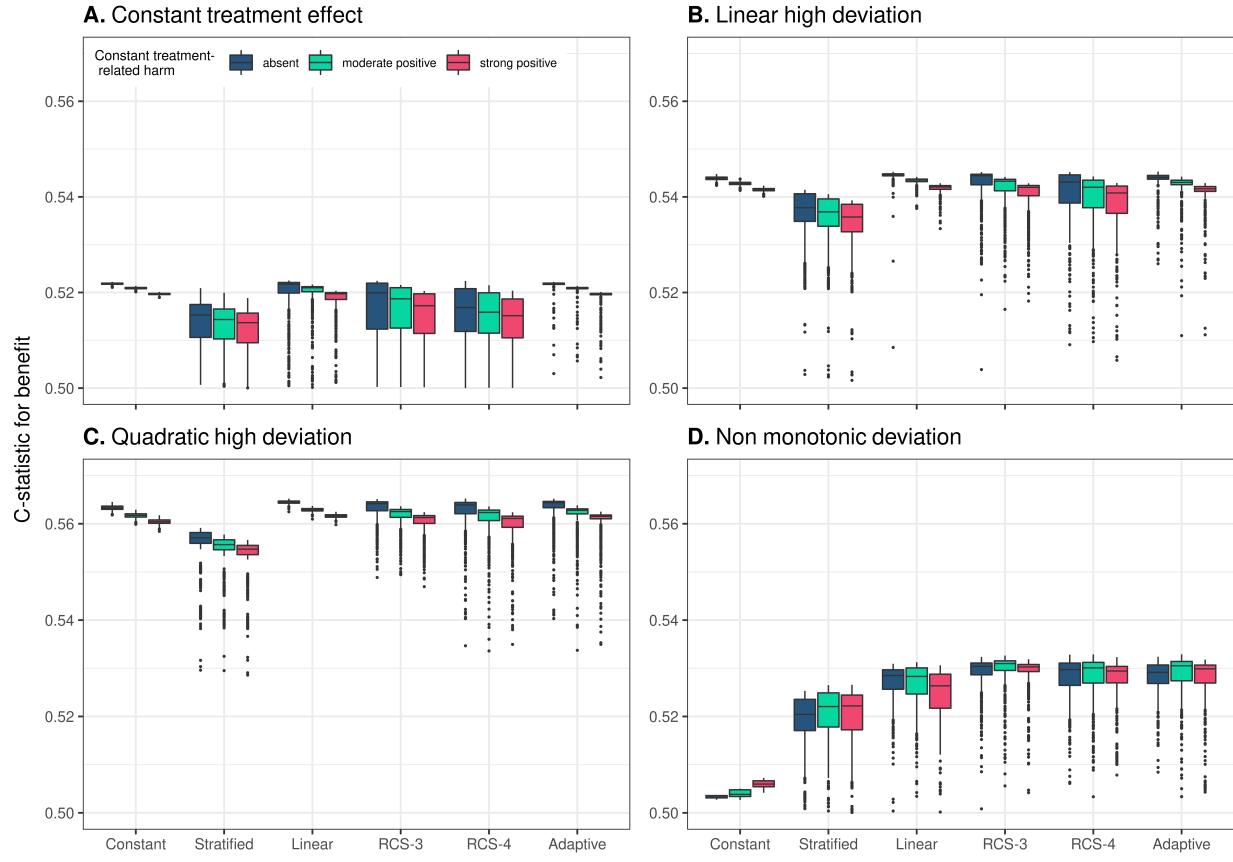


Figure 4: Discrimination for benefit of the considered methods across 500 replications calculated in a simulated sample of size 500,000. True prediction AUC of 0.75 and sample size of 4,250.

122 RCS methods (median AUC of 0.4971 for the constant effects model, 0.5285 for the linear interaction model and  
 123 0.5304 for the best-performing RCS-3; Figure 3; panel D). With increasing number of RCS knots, we observed  
 124 decreasing median values and increasing variability of the c-for-benefit in all scenarios. **With increasing sample**  
 125 **size... (Suppl Fig...)**

126 In terms of calibration for benefit, the constant effects model outperformed all other models in the scenario  
 127 with true constant treatment effects, but was miscalibrated for all deviation scenarios (Figure 5). The linear  
 128 interaction model showed best or close to best calibration across all scenarios and only showed worse calibration  
 129 compared to RCS-3 in case of non-monotonic deviations and treatment-related harms (Figure 5; panel D). The  
 130 adaptive approach was worse calibrated in scenarios with strong linear and non-monotonic deviations compared to  
 131 the linear interaction model and RCS-3. **With increasing sample size... (Supp Fig...)**

132 The results from all individual scenarios can be explored online at [https://arekkas.shinyapps.io/simulation\\_viewer/](https://arekkas.shinyapps.io/simulation_viewer/).

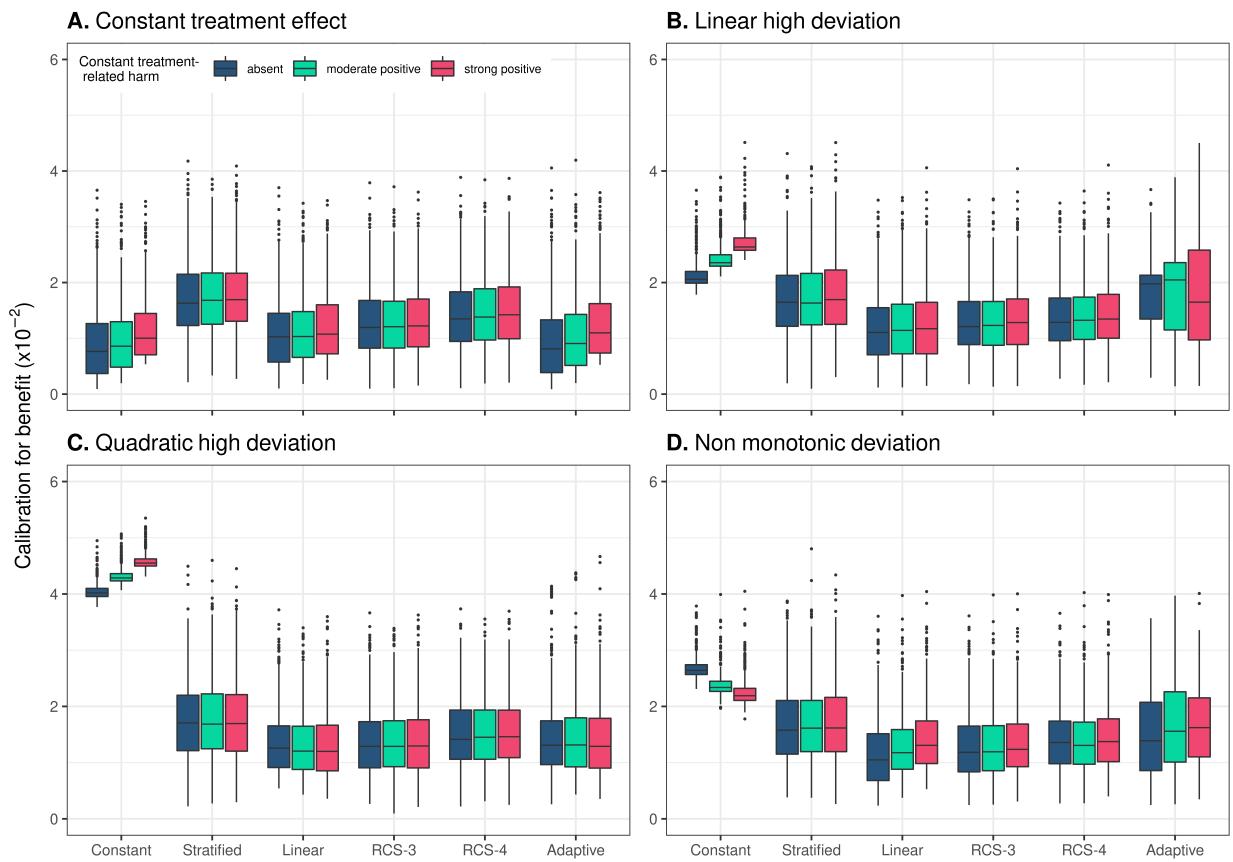


Figure 5: Calibration for benefit of the considered methods across 500 replications calculated in a simulated sample of size 500,000. True prediction AUC of 0.75 and sample size of 4,250.

134 **3.2. Case study**

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

139 In line with previous analyses [11,12], we fitted a logistic regression model with 6 baseline covariates, i.e. age,  
140 Killip class, systolic blood pressure, heart rate, an indicator of previous MI, and the location of MI, to predict  
141 30-day mortality risk. A constant effect of treatment was included in the model. When deriving risk predictions  
142 for individuals we set the treatment indicator to 0. More information on model development can be found in the  
143 supplement.

144 We used the risk linear predictor to fit the proposed methods under study for individualizing absolute benefit  
145 predictions. All methods predicted increasing benefits for patients with higher baseline risk predictions, but the  
146 fitted patterns were clearly different. The adaptive approach selected the model with RCS smoothing with 4 knots.  
147 However, for very low baseline risk the decreasing predicted benefit with increasing risk may be somewhat too  
148 flexible. The more robust models, the linear interaction model or the model with RCS smoothing (3 knots), gave  
149 very similar benefit predictions, followed the evolution of the stratified estimates very closely and may therefore  
150 be preferable for use in clinical practice. The linear interaction model had somewhat lower AIC compared to the  
151 model with RCS smoothing (3 knots), slightly better cross-validated discrimination (c-for-benefit 0.526 vs 0.525)  
152 and quite similar cross-validated calibration (ICI-for benefit 0.0115 vs 0.0117).

153 **4. Discussion**

154 The linear interaction model and the RCS-3 model both displayed very good performance under many of  
155 the considered simulation scenarios, in contrast with the constant relative treatment effect model. The linear  
156 interaction model was optimal in cases with smaller sample sizes and moderately performing baseline risk prediction  
157 models, that is, it had lower RMSE, was better calibrated for benefit and had better discrimination for benefit, even  
158 in scenarios with strong quadratic deviations. In scenarios with true non-monotonic deviations, the linear interaction  
159 model was outperformed by RCS-3, especially in the presence of true treatment-related harms. Increasing the sample  
160 size or the prediction model's discriminative ability favored RCS-3, especially in scenarios with non-monotonic  
161 deviations and in the presence of treatment-related harms.

162 RCS-4 and RCS-5 proved to be too flexible in all considered scenarios, as indicated by higher RMSE, increased  
163 variability of discrimination for benefit and worse calibration of benefit predictions. Even with larger sample sizes  
164 and strong quadratic or non-monotonic deviations from the base case scenario of constant relative treatment

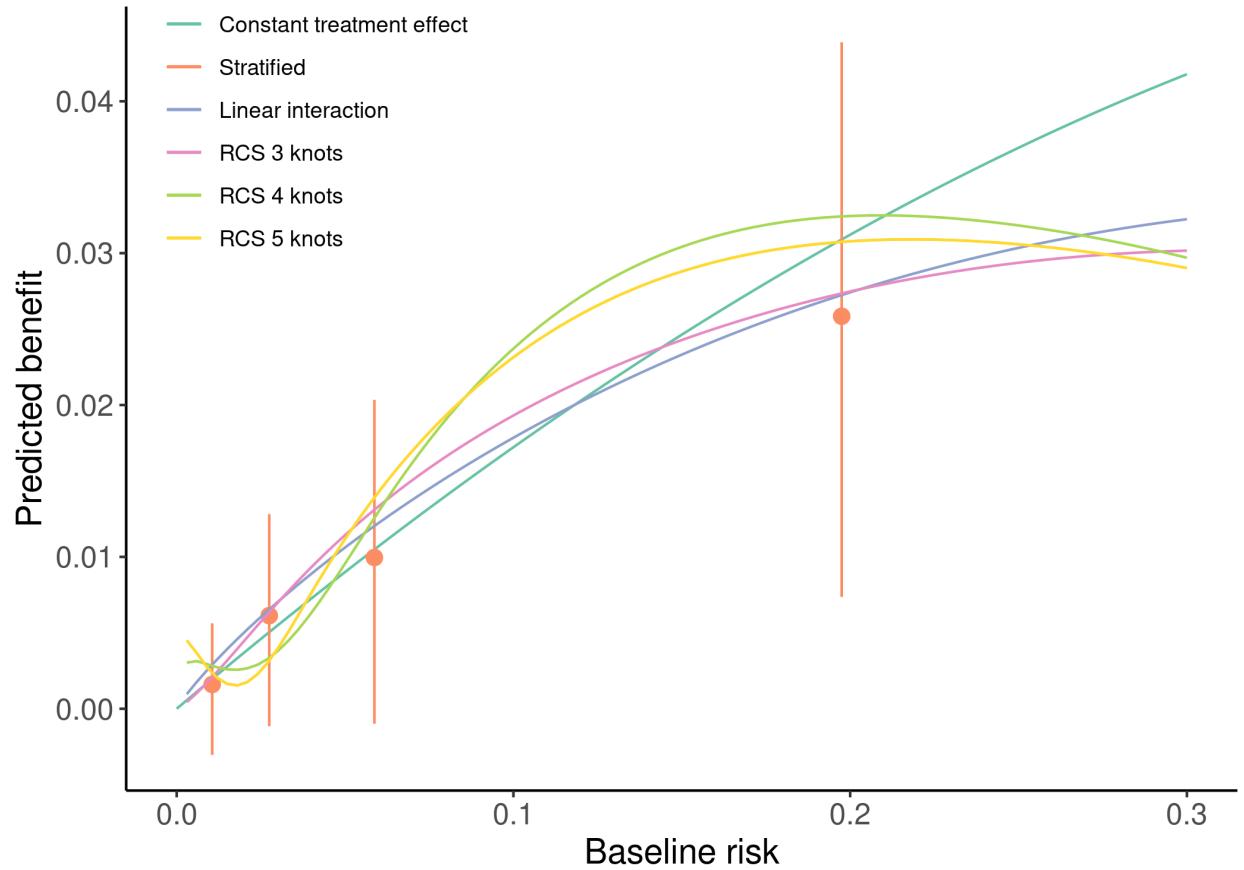


Figure 6: Individualized absolute benefit predictions based on baseline risk when using a constant treatment effect approach, a linear interaction approach and RCS smoothing using 3,4 and 5 knots. Risk stratified estimates of absolute benefit are presented within quartiles of baseline risk as reference.

165 effects, these more flexible restricted cubic splines did not outperform the simpler RCS-3 These approaches may  
166 only be helpful if we expect more extreme patterns of heterogeneous treatment effects compared to the quadratic  
167 deviations considered here.

168 The constant treatment effect model, despite having adequate performance in the presence of weak treatment  
169 effect heterogeneity on the relative scale, quickly broke down with stronger deviations from constant relative  
170 treatment effects. In these cases, the stratified approach generally had lower error rates compared to the constant  
171 treatment effect model. Stepwise treatment benefit estimates are very useful for demonstrating treatment effect  
172 heterogeneity—because estimating treatment effect requires groups of patients rather than individual patients—but  
173 are not helpful for making individualized absolute benefit predictions.

174 Increasing the discriminative ability of the risk model—by increasing the predictor coefficients of the true risk  
175 model—reduced RMSE for all methods. This increase in discriminative ability translates in higher variability of  
176 predicted risks, which, in turn, allows the considered methods to better capture absolute treatment benefits. As  
177 a consequence, the increase in discriminative ability of the risk model also led to higher values of c-for-benefit.  
178 Even though risk model performance is very important for the ability of risk-based methods to predict treatment  
179 benefit, prediction model development was outside the scope of this work and has already been studied extensively  
180 [5,13,14].

181 The adaptive approach had adequate performance, following closely on average the performance of the “true”  
182 model in most scenarios. However, with smaller sample sizes it tended to “miss” the treatment-risk interactions  
183 and selected simpler models (Supplementary Table S7). This resulted in increased RMSE variability in these  
184 scenarios, especially in the case of true strong linear or non-monotonic deviations from the base case scenario.  
185 Therefore, in the case of smaller sample sizes the simpler linear interaction model is a safer choice for predicting  
186 absolute benefits.

187 Risk-based approaches to predictive HTE estimate treatment benefit as a function of baseline risk. A limitation  
188 of our study is that we assumed treatment benefit to be a function of baseline risk in the majority of the simulation  
189 scenarios. We attempted to address that by introducing constant moderate and strong treatment-related harms,  
190 applied on the absolute scale. Also, we considered a small number of scenarios with true treatment-covariate  
191 interactions, in which our main conclusions remained the same (Supplement, XX). Future simulation studies could  
192 explore the effect of more extensive deviations from risk-based treatment effects.

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

198 other.

199 In conclusion, the linear interaction approach is a viable option with smaller sample sizes and/or moderately  
200 performing risk prediction modelsRCS-3 is a better option when non-monotonic deviations from a constant relative  
201 treatment effect and/or substantial treatment-related harms are anticipated. With larger sample size, an adaptive  
202 approach – selecting the method with optimal AIC – can also be considered as an automated alternative.

203 **5. References**

- 204 [1] Varadhan R, Segal JB, Boyd CM, Wu AW, Weiss CO. A framework for the analysis of heterogeneity of  
205 treatment effect in patient-centered outcomes research. *Journal of Clinical Epidemiology* 2013;66:818–25.  
206 <https://doi.org/10.1016/j.jclinepi.2013.02.009>.
- 207 [2] Rekkas A, Paulus JK, Raman G, Wong JB, Steyerberg EW, Rijnbeek PR, et al. Predictive approaches  
208 to heterogeneous treatment effects: A scoping review. *BMC Medical Research Methodology* 2020;20:  
209 <https://doi.org/10.1186/s12874-020-01145-1>.
- 210 [3] Kent DM, Paulus JK, Klaveren D van, D'Agostino R, Goodman S, Hayward R, et al. The predictive  
211 approaches to treatment effect heterogeneity (PATH) statement. *Annals of Internal Medicine* 2019;172:35.  
212 <https://doi.org/10.7326/m18-3667>.
- 213 [4] Kent DM, Klaveren D van, Paulus JK, D'Agostino R, Goodman S, Hayward R, et al. The predictive approaches  
214 to treatment effect heterogeneity (PATH) statement: Explanation and elaboration. *Annals of Internal Medicine*  
215 2019;172:W1. <https://doi.org/10.7326/m18-3668>.
- 216 [5] Klaveren D van, Balan TA, Steyerberg EW, Kent DM. Models with interactions overestimated heterogeneity of  
217 treatment effects and were prone to treatment mistargeting. *Journal of Clinical Epidemiology* 2019;114:72–83.  
218 <https://doi.org/10.1016/j.jclinepi.2019.05.029>.
- 219 [6] Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in  
220 treatment effects in clinical trials: A proposal. *Trials* 2010;11. <https://doi.org/10.1186/1745-6215-11-85>.
- 221 [7] Kent DM, Nelson J, Dahabreh IJ, Rothwell PM, Altman DG, Hayward RA. Risk and treatment effect  
222 heterogeneity: Re-analysis of individual participant data from 32 large clinical trials. *International Journal of  
223 Epidemiology* 2016;dyw118. <https://doi.org/10.1093/ije/dyw118>.
- 224 [8] Harrell FE, Lee KL, Pollock BG. Regression models in clinical studies: Determining relationships between  
225 predictors and response. *JNCI Journal of the National Cancer Institute* 1988;80:1198–202. <https://doi.org/10.1093/jnci/80.15.1198>.
- 227 [9] Klaveren D van, Steyerberg EW, Serruys PW, Kent DM. The proposed “concordance-statistic for benefit”  
228 provided a useful metric when modeling heterogeneous treatment effects. *Journal of Clinical Epidemiology*  
229 2018;94:59–68. <https://doi.org/10.1016/j.jclinepi.2017.10.021>.
- 230 [10] Austin PC, Steyerberg EW. The integrated calibration index (ICI) and related metrics for quantifying the  
231 calibration of logistic regression models. *Statistics in Medicine* 2019;38:4051–65. <https://doi.org/10.1002/sim.8281>.
- 233 [11] Califf RM, Woodlief LH, Harrell FE, Lee KL, White HD, Guerci A, et al. Selection of thrombolytic  
234 therapy for individual patients: Development of a clinical model. *American Heart Journal* 1997;133:630–9.

- 235            [https://doi.org/10.1016/s0002-8703\(97\)70164-9](https://doi.org/10.1016/s0002-8703(97)70164-9).
- 236 [12] Steyerberg EW, Bossuyt PMM, Lee KL. Clinical trials in acute myocardial infarction: Should we adjust  
237 for baseline characteristics? *American Heart Journal* 2000;139:745–51. [https://doi.org/10.1016/s0002-8703\(00\)90001-2](https://doi.org/10.1016/s0002-8703(00)90001-2).
- 239 [13] Burke JF, Hayward RA, Nelson JP, Kent DM. Using internally developed risk models to assess heterogeneity  
240 in treatment effects in clinical trials. *Circulation: Cardiovascular Quality and Outcomes* 2014;7:163–9.  
241 <https://doi.org/10.1161/circoutcomes.113.000497>.
- 242 [14] Abadie A, Chingos MM, West MR. Endogenous stratification in randomized experiments. *The Review of  
243 Economics and Statistics* 2018;100:567–80. [https://doi.org/10.1162/rest\\_a\\_00732](https://doi.org/10.1162/rest_a_00732).
- 244 [15] Athey S, Tibshirani J, Wager S. Generalized random forests. *The Annals of Statistics* 2019;47. <https://doi.org/10.1214/18-aos1709>.
- 246 [16] Lu M, Sadiq S, Feaster DJ, Ishwaran H. Estimating individual treatment effect in observational data  
247 using random forest methods. *Journal of Computational and Graphical Statistics* 2018;27:209–19. <https://doi.org/10.1080/10618600.2017.1356325>.
- 249 [17] Wager S, Athey S. Estimation and inference of heterogeneous treatment effects using random forests. *Journal  
250 of the American Statistical Association* 2018;113:1228–42. <https://doi.org/10.1080/01621459.2017.1319839>.