

Appendix C. PCATS Aim 1b: 2-Stage Treatment Assignment Results

PCATS Aim 1b:
Two-stage treatment
assignment results

Two-Stage Simulation Study Results

After making sure the performances of the GPMatch in the one-stage setting, we extended the GPMatch and the BART for the two-staged ATS. Five different simulation studies are performed. Since the primary goal of the study is to evaluate the performance of 2-stage BART and GPMatch for estimating the averaged treatment effort for ATS, four simulation designs were considered a sequential, multiple assignment, randomized trial (SMART), where the treatment is assigned at random at the 1st stage; the 2nd stage treatment is assigned adaptive to the patient's responses to the previous treatment. The design also considered heterogeneous treatment effect setting. Specifically, the five sets of simulation studies are:

1. A SMART trial with nonlinear outcome and treatment model.
2. A SMART trial with including an unmeasured binary confounder (U_0) at the baseline, and linear outcome and treatment model.
3. A SMART trial modified based on Kang and Schafer's dual misspecification setting.
4. A SMART trial with the 1st stage disease outcome modifies the 2nd stage treatment effects, a linear model setting.
5. Observational study subgroup treatment effect at both stages, a nonlinear setting.

In all setting, we consider the observed outcomes are measured without error. That is at the end of the 1st stage, the observed outcomes at the end of the 1st stage of treatment (L_1) is determined by

$$L_1 = A_0 L_1(1) + (1 - A_0) L_1(0)$$

Then, at the end of 2nd stage, the observed outcome (Y) is determined by

$$Y = A_0 A_1 Y(1,1) + (1 - A_0) A_1 Y(0,1) + A_0 (1 - A_1) Y(1,0) + (1 - A_0) (1 - A_1) Y(0,0).$$

Without loss of generality, the simulation study considered a binary treatment decisions. The treatment assignment at the initial decision point (A_0) is determined by the baseline covariates (X). The treatment at the end of 1st stage (A_1) is assignment based on the observed patient's responses L_1 , previous treatment assignment (A_0) and the baseline covariates (X), i.e. $[A_1 | A_0, X, L_1]$. The potential outcomes at the end of 1st stage is determined by the baseline covariates (X). The potential outcomes at the end of 2nd stage is determined by the baseline covariates and the potential outcomes at end of the 1st stage, i.e. $[Y(00), Y(01), Y(10), Y(11) | X, L_1(0), L_1(1)]$. Under the ATS, there are two types of confounders - X denotes the baseline confounder, which may include age, gender, race, insurance status, baseline disease severity and health related quality of life; the L_1 is a time-varying confounder, which may include disease severity and health at the end of 1st stage. Of note, the L_1 may include the intermediate outcome measure, e.g. disease severity.

The recent paper by Newsome, Keogh and Daniel (2018) presented the most comprehensive review of six existing methods currently used for the evaluating causal treatment effects of ATS.

1. IPW: Invers probability weighting of marginal structural model, where the weight is the inverse of joint probability of treatment assignment $[A_0, A_1|X]$;
2. IPW(truncated): same as the IPW, with the PS truncated at 0.1 and 0.99;
3. HA-MSM: history-adjusted marginal structural models (MSM) $[Y(a_0, a_1)|X]$, where the weight is the inverse of joint time-varying PS $[A_0, A_1|X, L_1] = [A_0|X] \times [A_1|A_0, X, L_1]$.
4. HA-MSM(truncated): same as the HA-MSM, with the stabilized weight truncated at the 1st and 99th percentile;
5. G-computation: G-computatoin approaches impute the missing potential outcome similarly as the missing imputation chained equation (MICE), imputing $[Y(a_0, a_1)|X, L_1(a_0)]$ and $[L_1|X]$ using the observed outcomes and covariates.
6. G-estimation: g-estimation includes the PS estimates at each decision point into the structural nested model $[Y(a_0, a_1)|X, L_1(a_0)]$, and solve the corresponding estimating equation.

The authors reported persistent weaker performances of IPW method compared to the HA-MSM methods. Thus they are not considered in our study. The simulation studies compared the rest four methods against both 2-stage BART and the 2-stage GPMatch in our simulation studies.

For the 2-stage ATS (A_0, A_1) , there are 4 causal treatment effect of ATS, $\{\tau_1, \psi_1, \psi_2, \psi_3\}$ which are defined by the six potential outcomes $(L_1(0), L_1(1), Y(00), Y(01), Y(10), Y(11))$:

$$L_1(a_0) = L_1(0) + \tau_1 a_0;$$

$$Y(a_0 a_1) = Y(00) + \psi_1 a_0(1 - a_1) + \psi_2 a_1(1 - a_0) + \psi_3 a_0 a_1.$$

Thus, the τ_1 is the 1st line treatment effect at the end of the 1st stage:

$$\tau_1 = L_1(1) - L_1(0);$$

The $\{\psi_1, \psi_2, \psi_3\}$ is the 2nd line treatment effect of ATS (a_0, a_1) at the end of 2nd stage. Thus the all pairwise comparisons of the four 2nd stage potential outcomes can be written as:

$$Y(10) - Y(00) = \psi_1; Y(01) - Y(00) = \psi_2; Y(11) - Y(00) = \psi_3;$$

$$Y(10) - Y(01) = \psi_2 - \psi_1; Y(11) - Y(01) = \psi_3 - \psi_1; Y(11) - Y(10) = \psi_3 - \psi_2.$$

The simulation results are summarized for each of the 7 causal contrast of ATS at both stages. All simulation results are summarized over 200 replicates. The root mean square error (RMSE) and median absolute error (MAE) are summarized over all replicates and plotted for all method of comparisons. For GPMath and BART, histogram of the posterior estimates are plotted.

1. A SMART Trial Nonlinear Model Setting

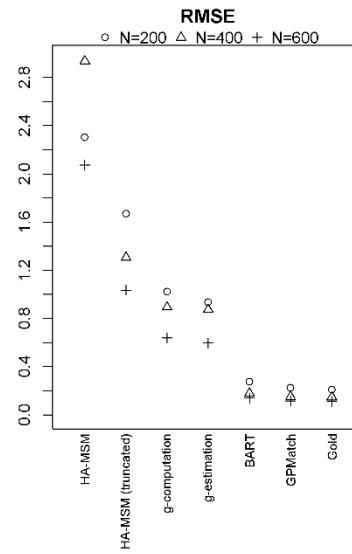
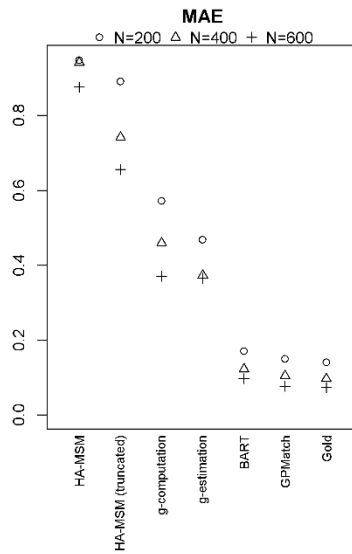
This simulation resembles a SMART trial setting, where the initial treatment is assigned at random. The stage 1 treatment has no effect on the disease progress at the end of 1st stage treatment. Both models of treatment assignment at the 2nd stage and the potential outcomes are nonlinear functions of the end of 1st stage responses L_1 ,

$$X \sim \text{Bernoulli}(0.4), \quad A_0 \sim \text{Bernoulli}(0.5), \quad L_1 \sim N(0,1)$$

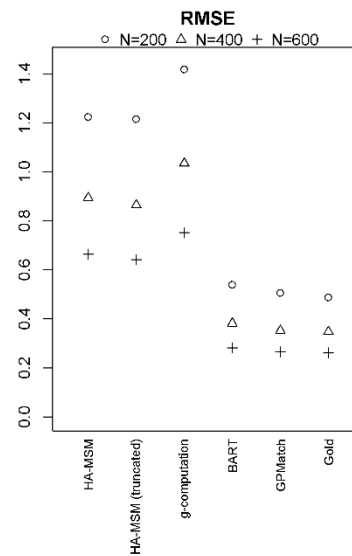
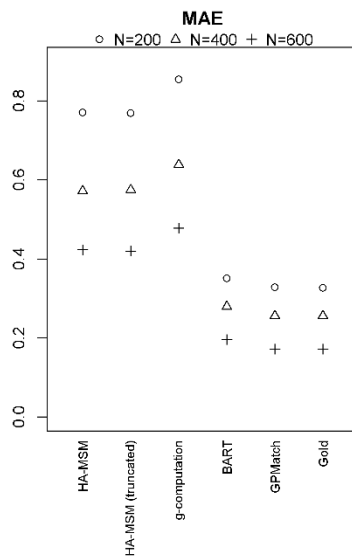
$$A_1 | L_1, A_0, X \sim \text{Bernoulli}(\text{expit}(0.2 - 0.2A_0 + L_1^{1/3}))$$

$$Y(a_0, a_1) \sim N(-2 + 2.5a_0 + 3.5a_1 + 0.5a_0a_1 - 3 \exp(-L_1), sd = 1).$$

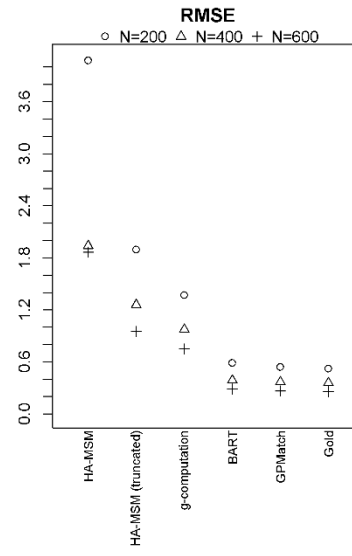
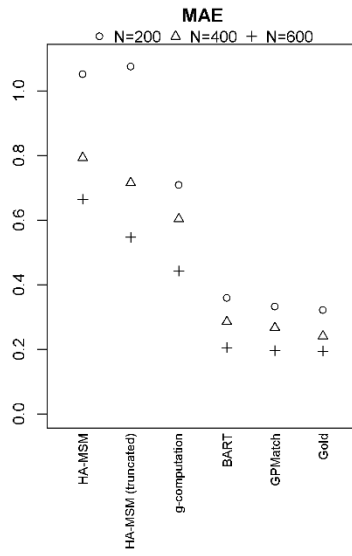
Y01-Y00



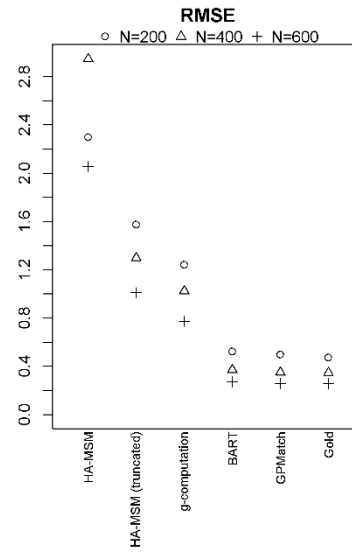
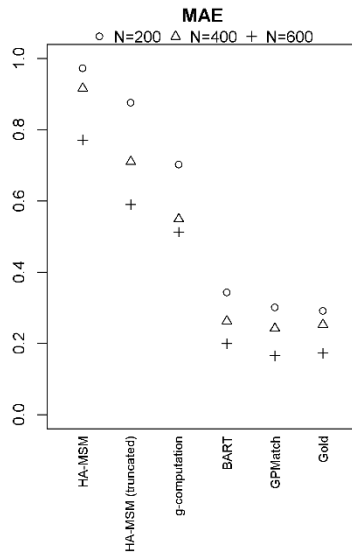
Y10-Y00



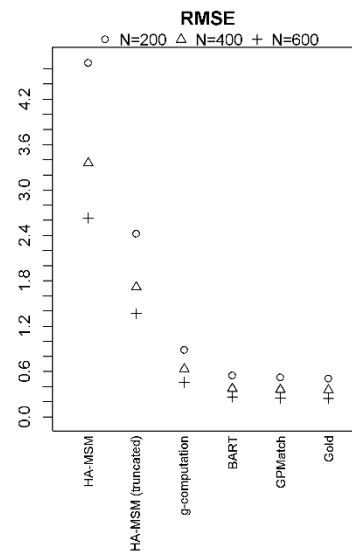
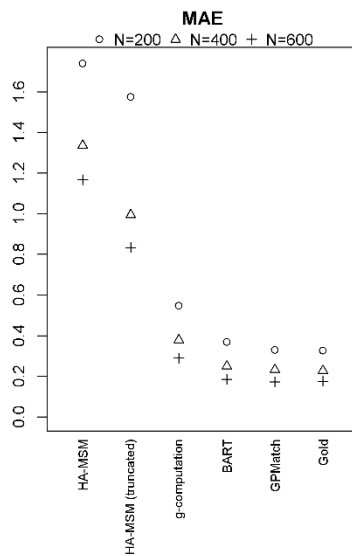
Y11-Y00



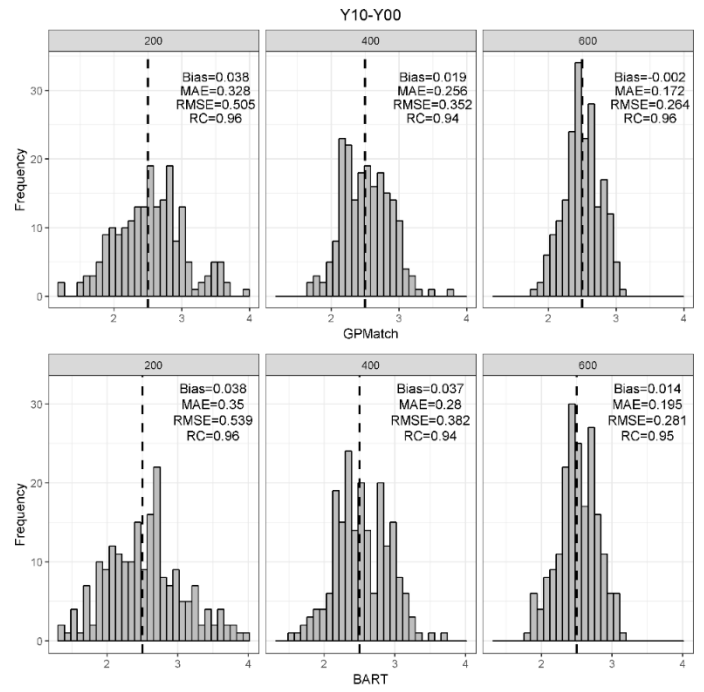
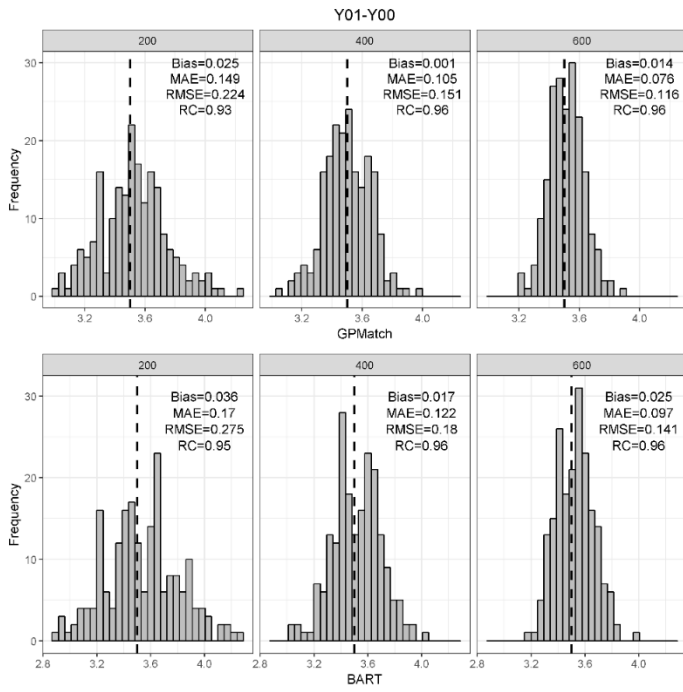
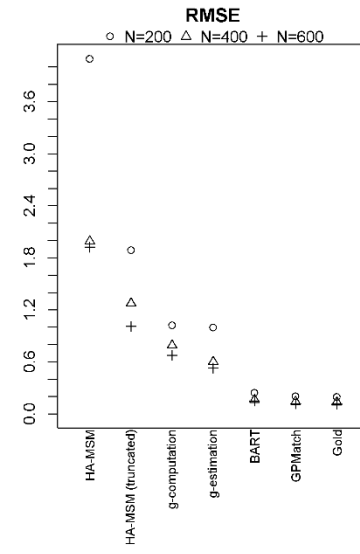
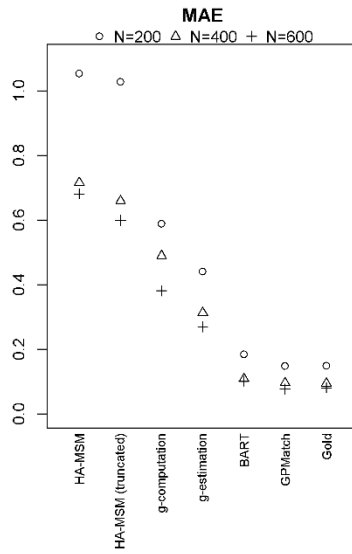
Y10-Y01

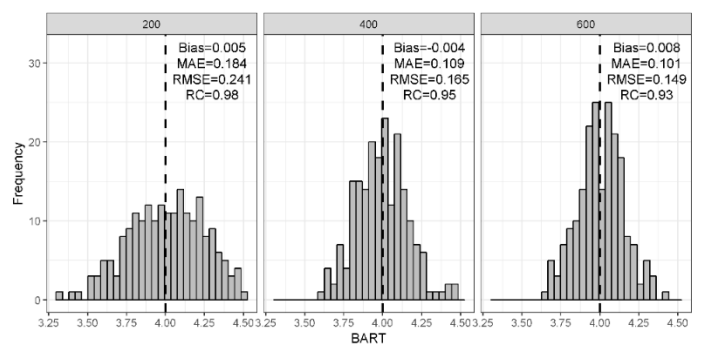
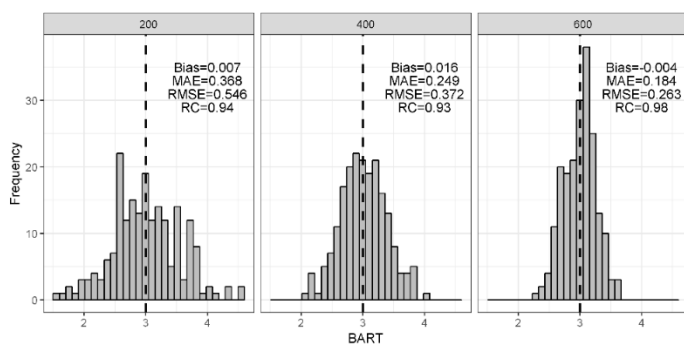
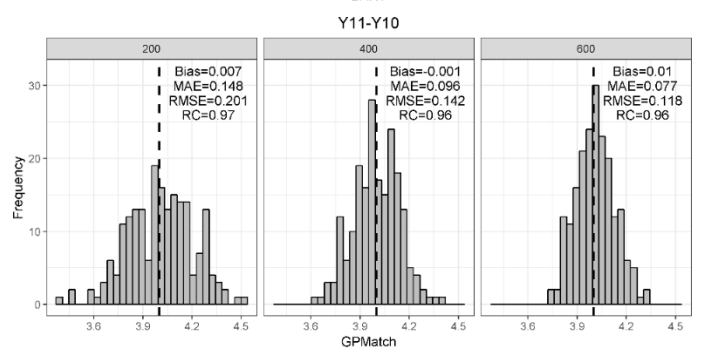
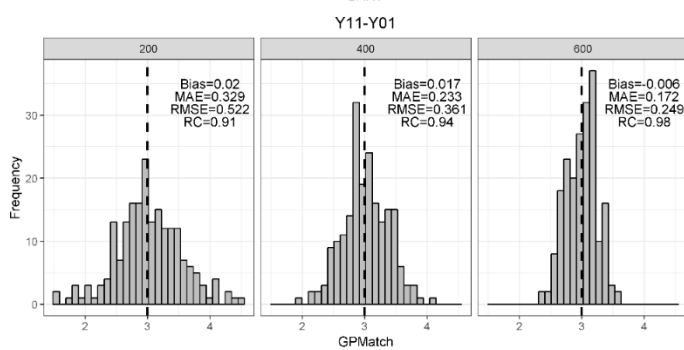
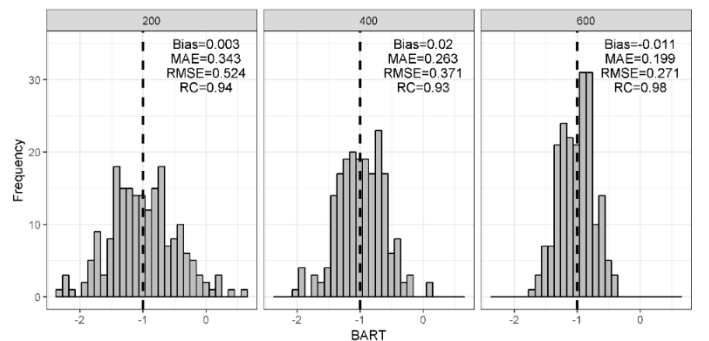
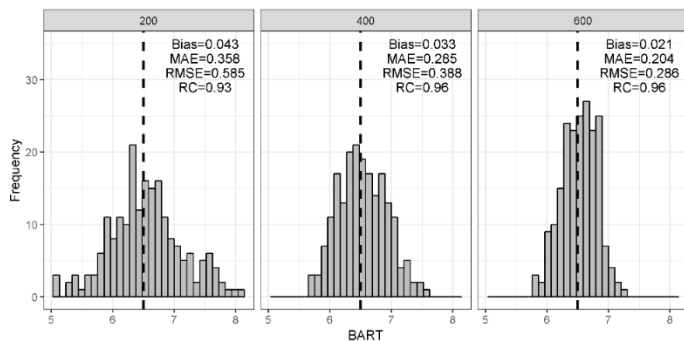
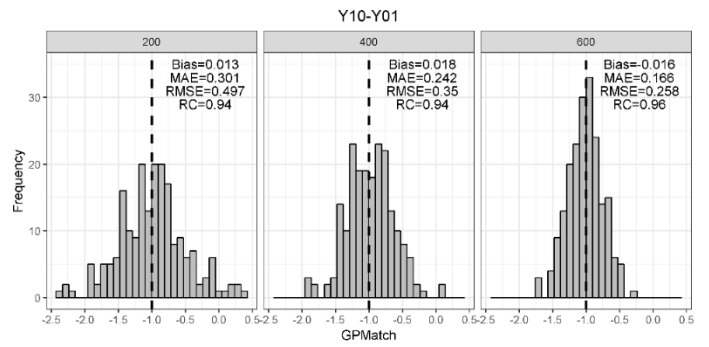
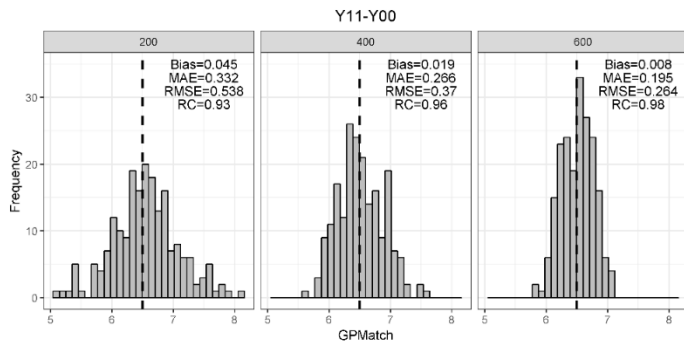


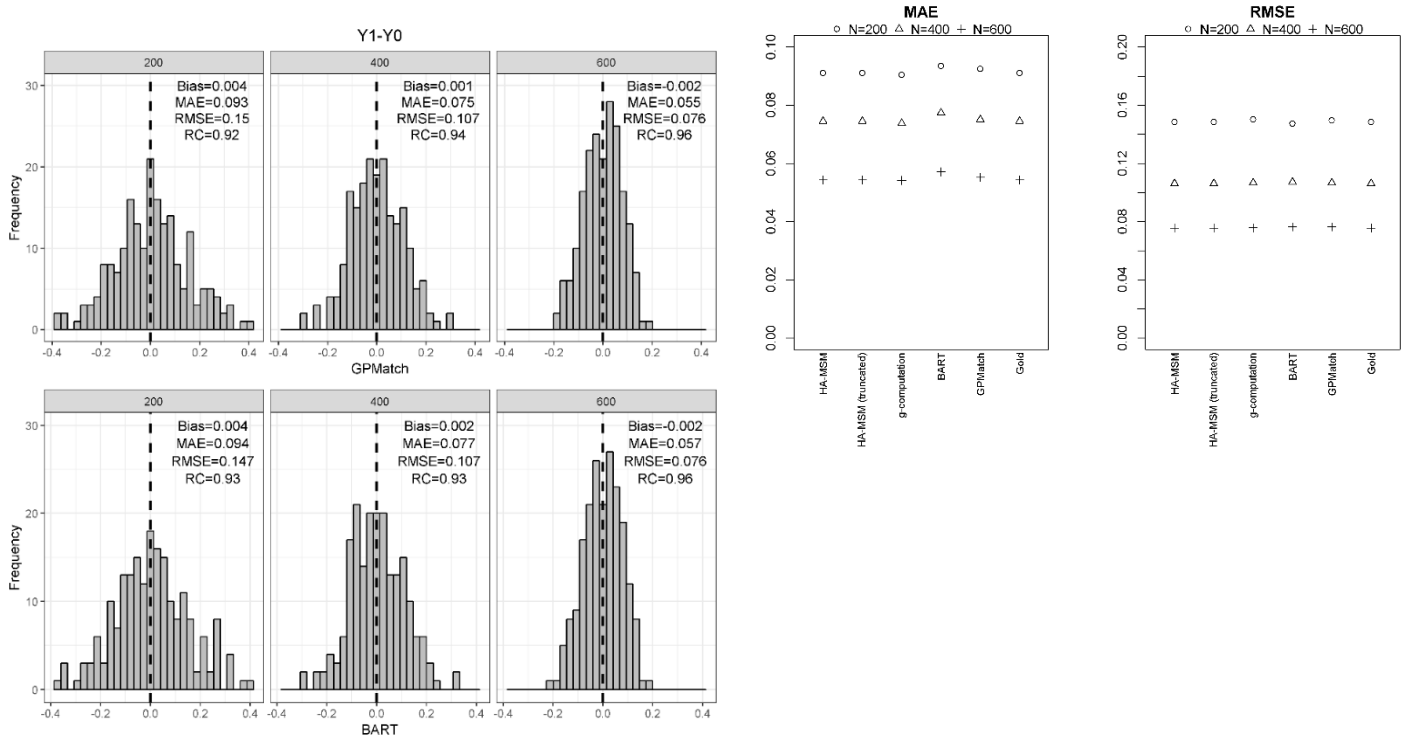
Y11-Y01



Y11-Y10







2. A SMART Trial Linear Model, Unmeasured Covariate Setting

Following a setting used in Daniels (2013), this simulation considered an unmeasured confounder U_0 . Specifically, the data are simulated according to the following setup:

$$U_0 \sim \text{Bernoulli}(0.4),$$

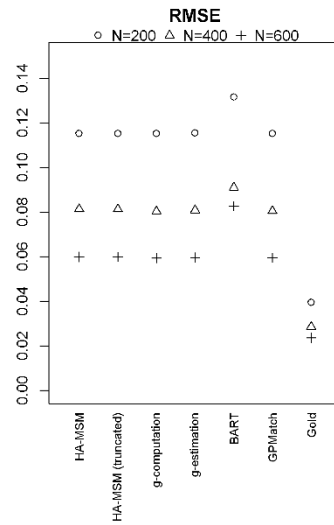
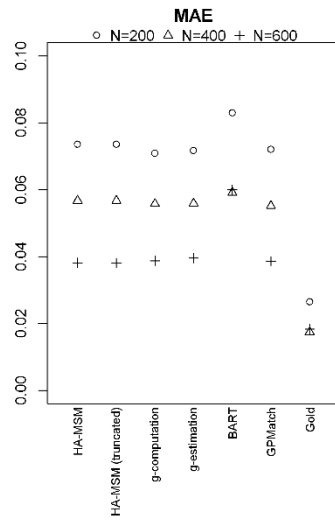
$$A_0 \sim \text{Bernoulli}(0.5),$$

$$L_1(a_0) \sim \text{Bernoulli}(\text{expit}(0.25 + 0.3a_0 - 0.2U_0 - 0.05a_0U_0))$$

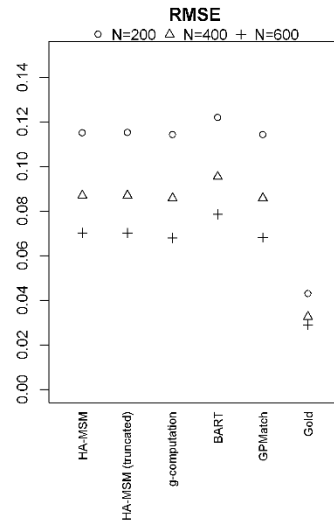
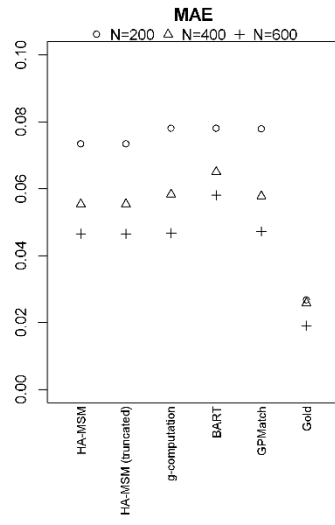
$$A_1 \sim \text{Bernoulli}(\text{expit}(0.4 + 0.5A_0 - 0.3L_1 - 0.4A_0L_1))$$

$$Y(a_0, a_1) \sim N(0.25 - 0.5a_0 - 0.75a_1 + 0.2a_0a_1 - U_0, 0.2)$$

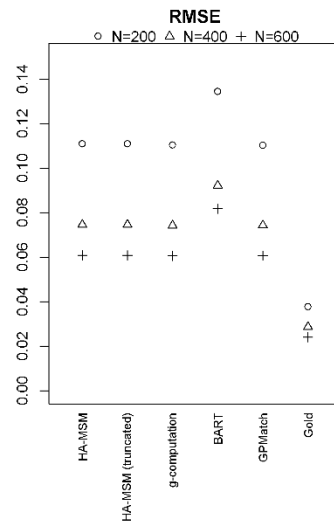
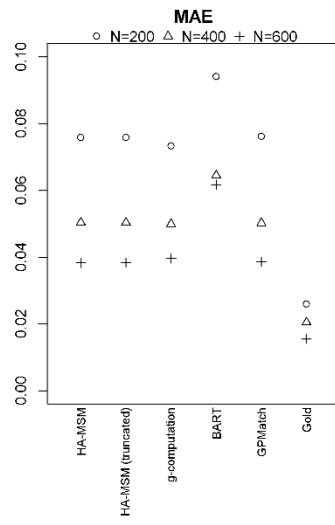
Y01-Y00



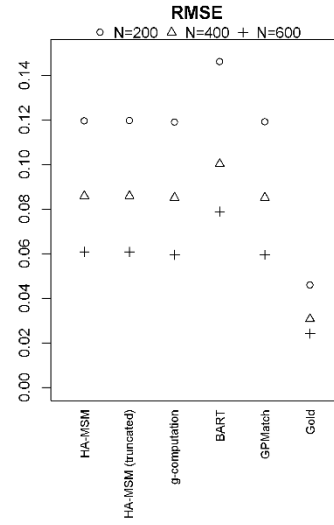
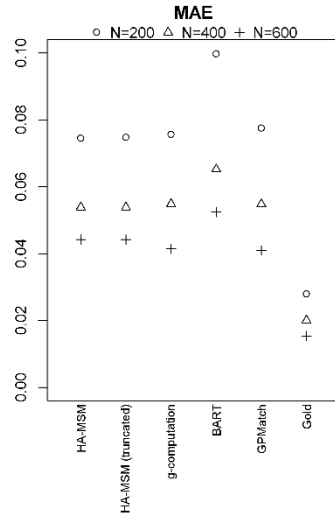
Y10-Y00



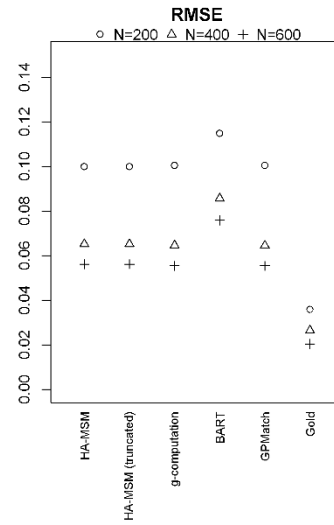
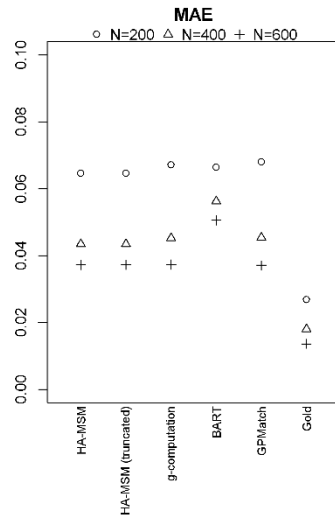
Y11-Y00



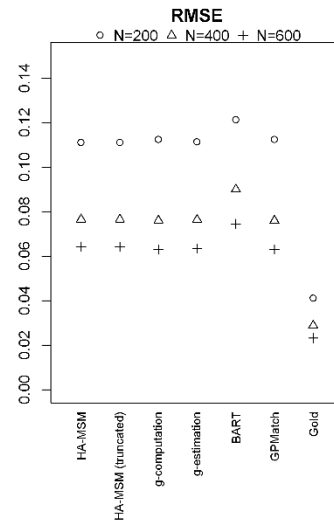
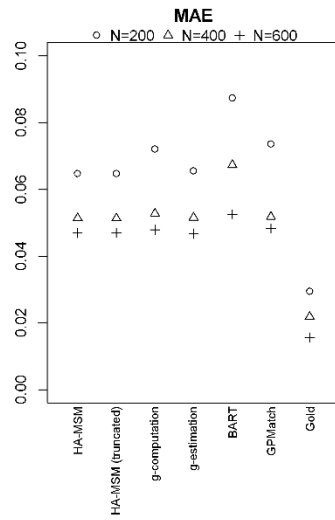
Y10-Y01

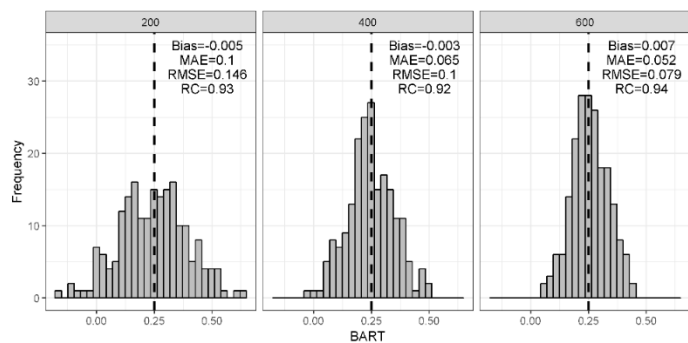
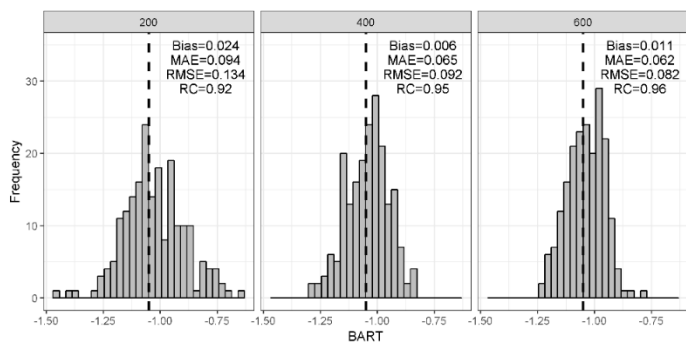
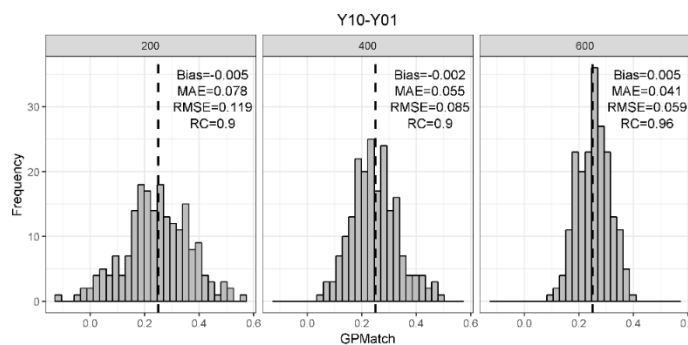
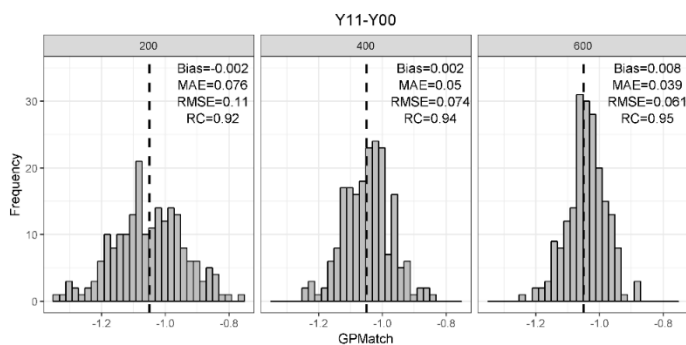
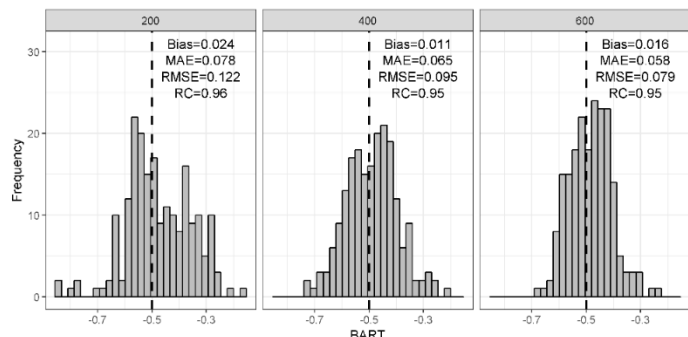
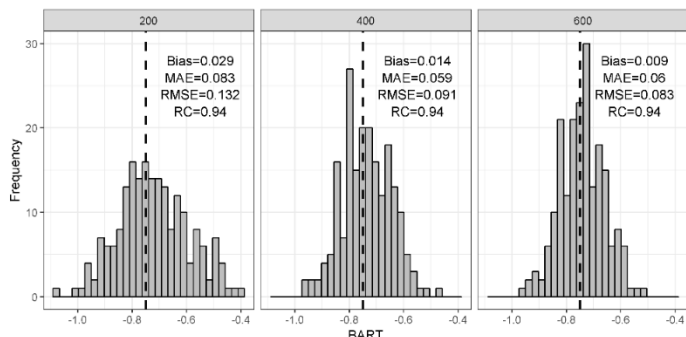
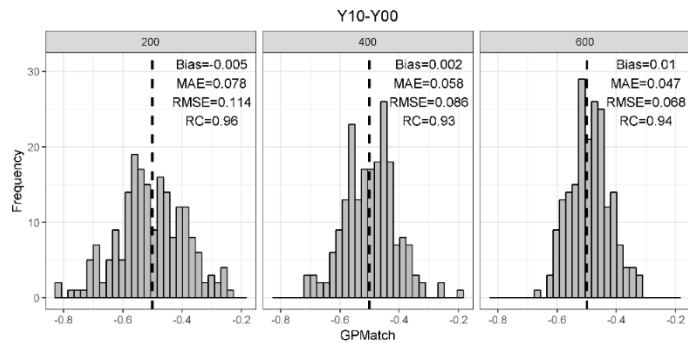
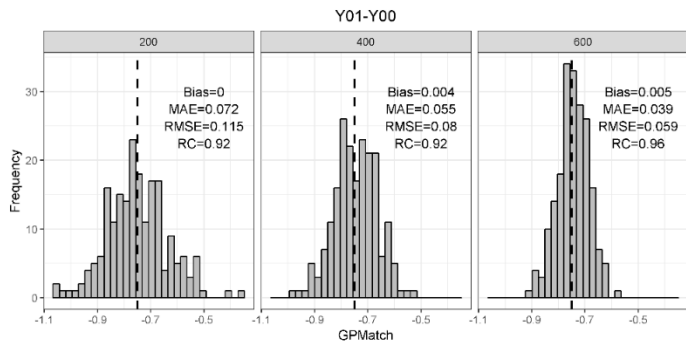


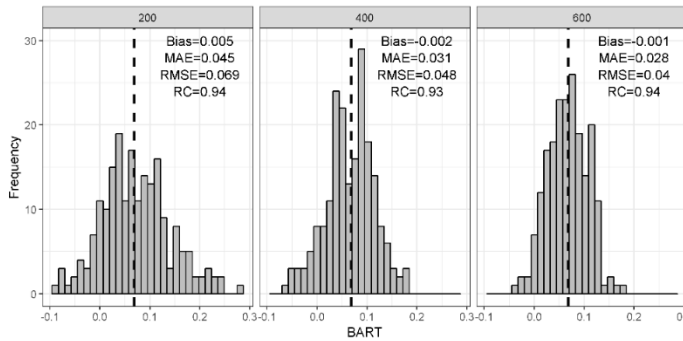
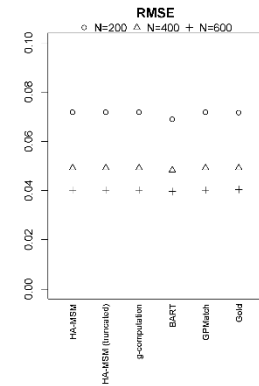
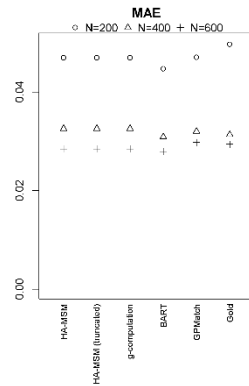
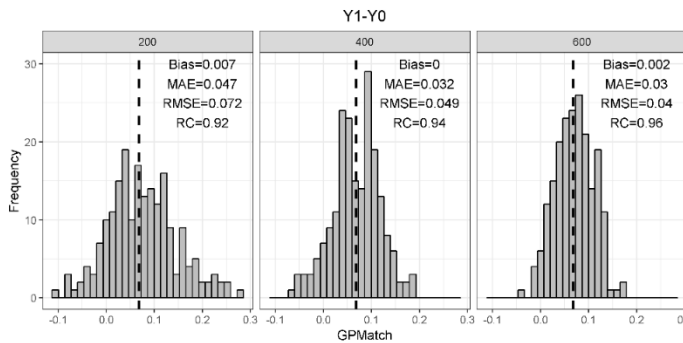
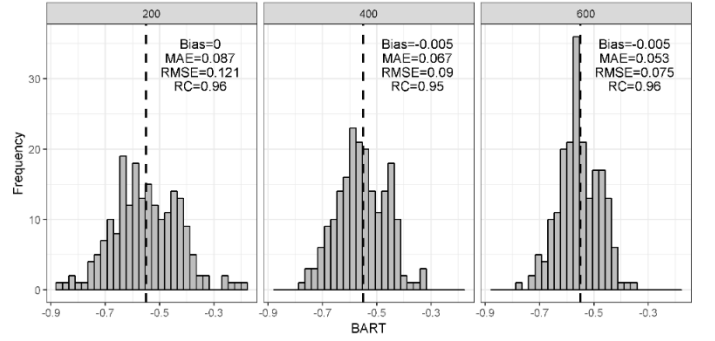
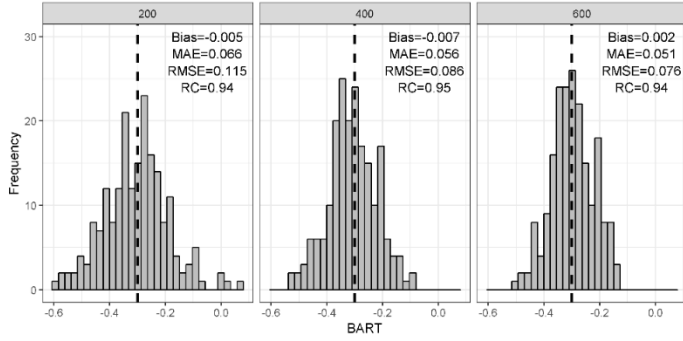
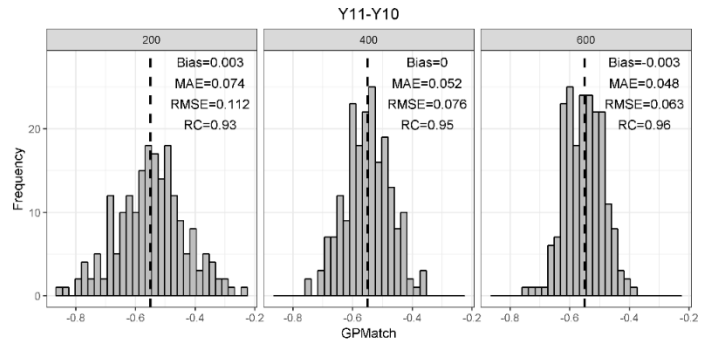
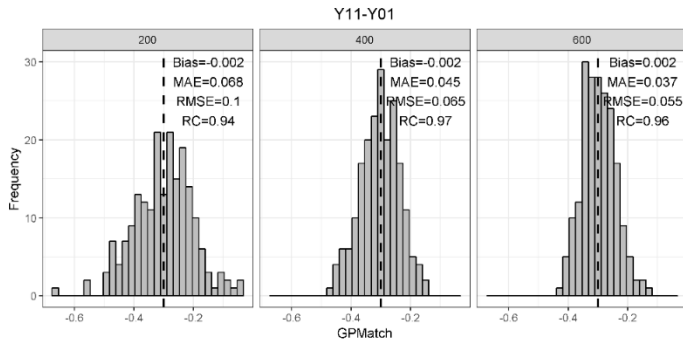
Y11-Y01



Y11-Y10







3. A SMART Trial Kang and Schafer Dual Misspecification Setting

We extended the well-known Kang and Schafer (2014) simulation to a 2-stage setting. Like the SMART trial, the 1st treatment is assigned at random, and the outcome at is a linear function of the baseline covariates $Z_1 - Z_4$.

$$Z_1, Z_2, Z_3, Z_4 \sim N(0,1), A_0 \sim \text{Bernoulli}(0.5)$$

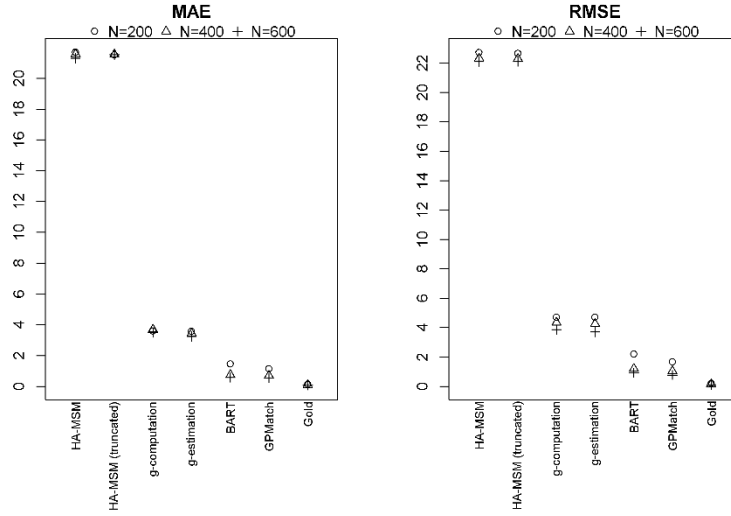
$$L_1 \sim N(-1.5 + 27.4Z_1 + 13.7Z_2 + 0 * Z_3 + 0 * Z_4 - 3A_0, 1)$$

$$A_1 \sim \text{Bernoulli}(\text{expit}(0.25A_0 + (0.1) * L_1^{1/3} + 0.75 * (Z_1 - 0.5Z_2 + 0.25Z_3 + 0.1Z_4)))$$

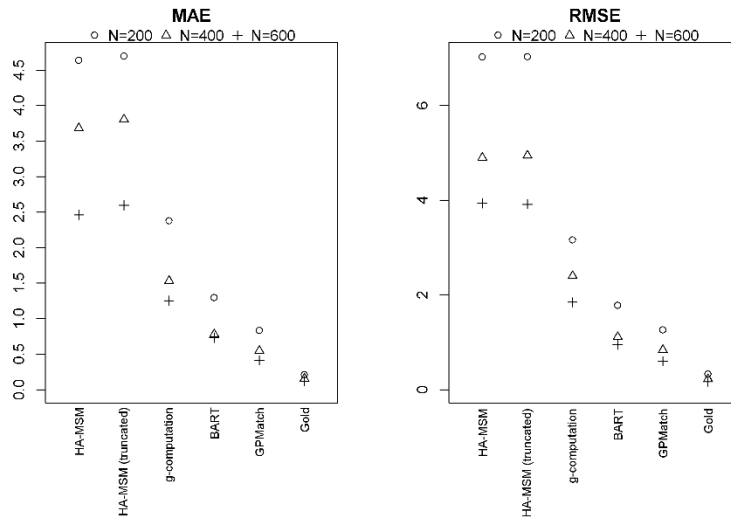
$$Y(A_0, A_1) \sim N(210 + L_1 + 13.7Z_3 + 13.7Z_4 - 5A_0 - 3A_1 - 2A_0A_1, 1)$$

Like in Kang and Schafer, only transformed covariates are observed $x_1 = \exp(z_1/2), x_2 = z_2/(1 + \exp(z_1)) + 10, x_3 = \left(\frac{z_1 z_3}{25} + 0.6\right)^3$, and $x_4 = (z_2 + z_4 + 20)^2$.

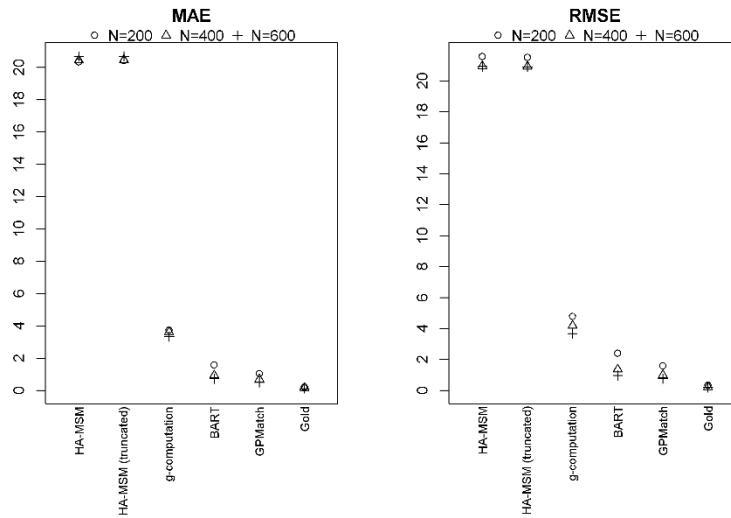
Y01-Y00



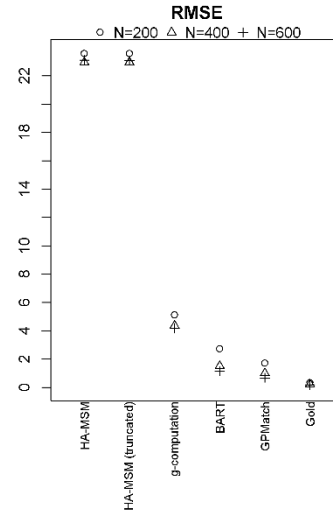
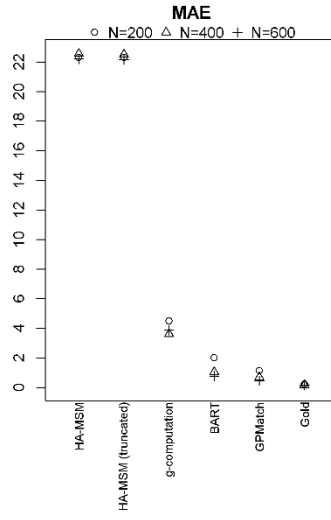
Y10-Y00



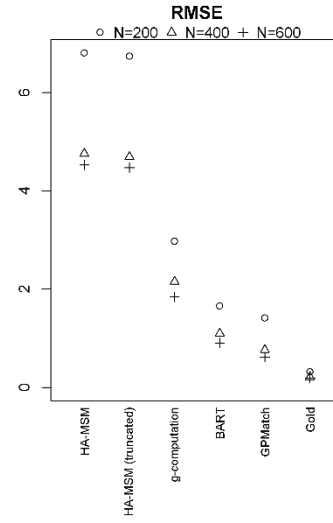
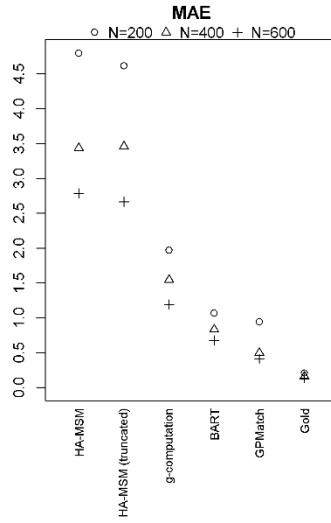
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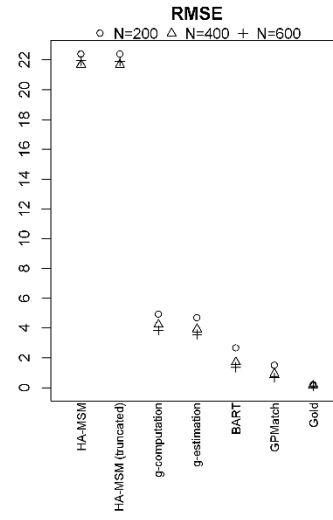
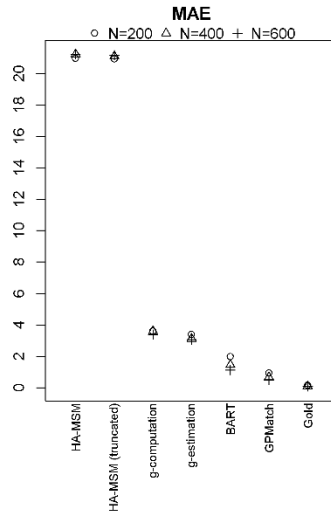
Y10-Y01



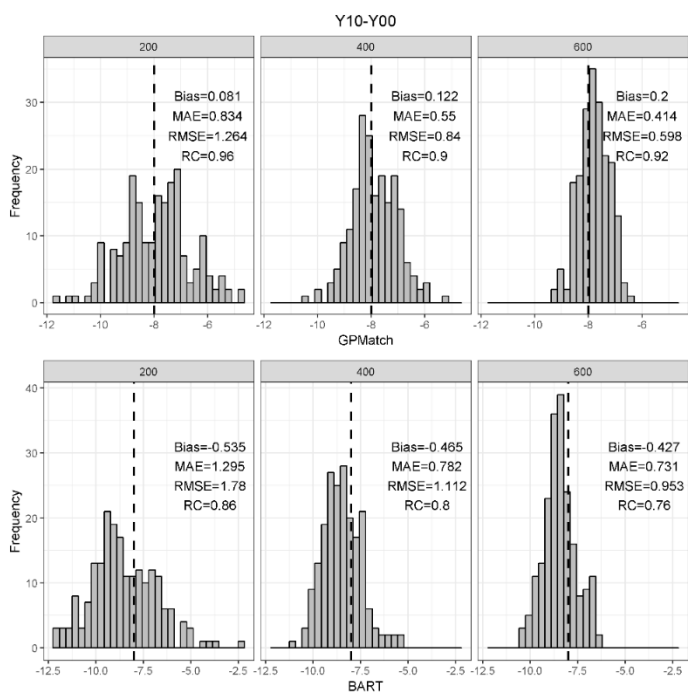
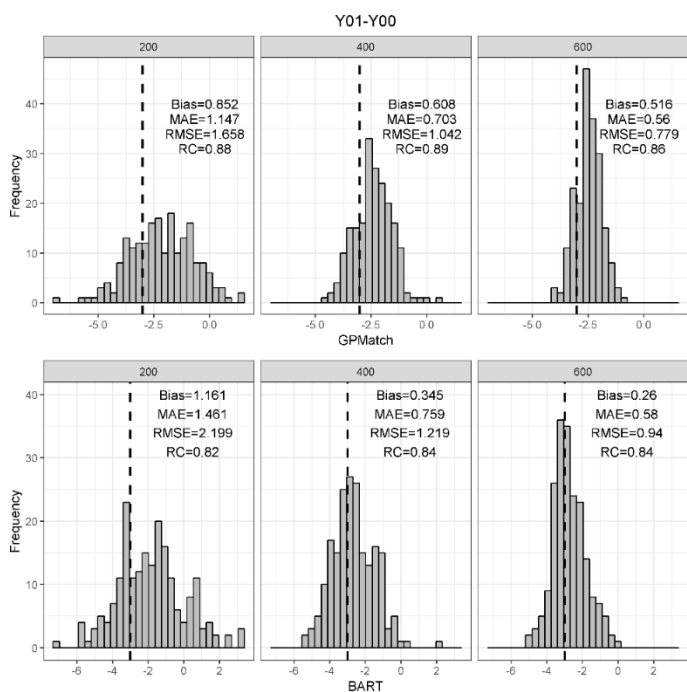
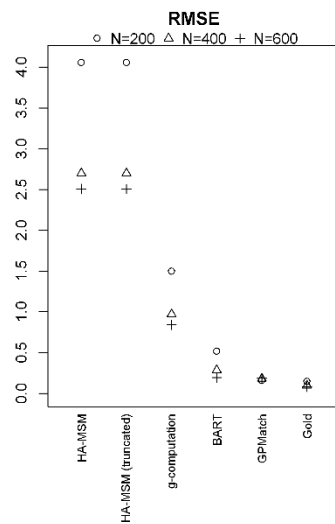
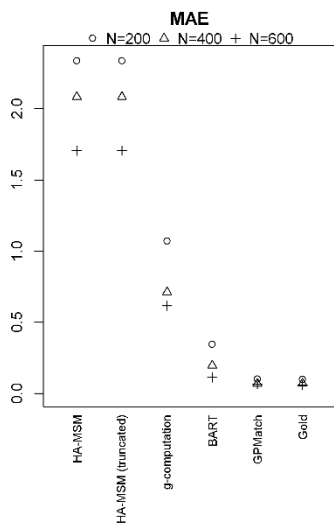
Y11-Y01

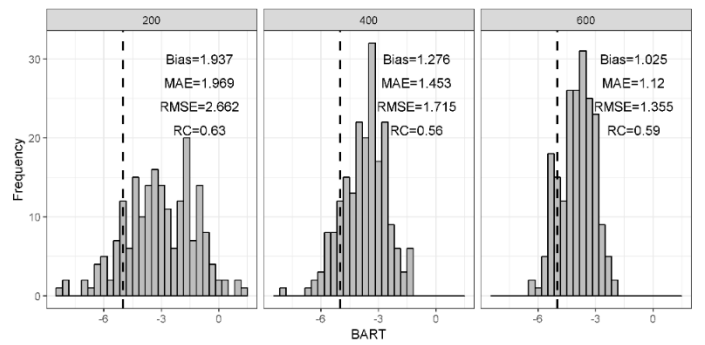
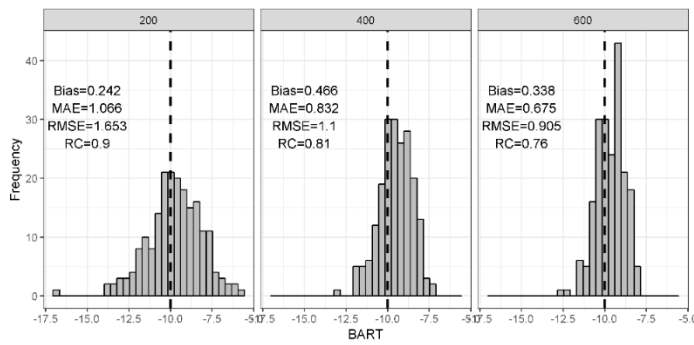
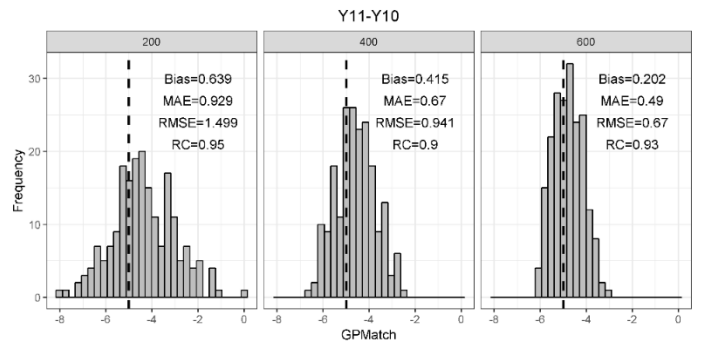
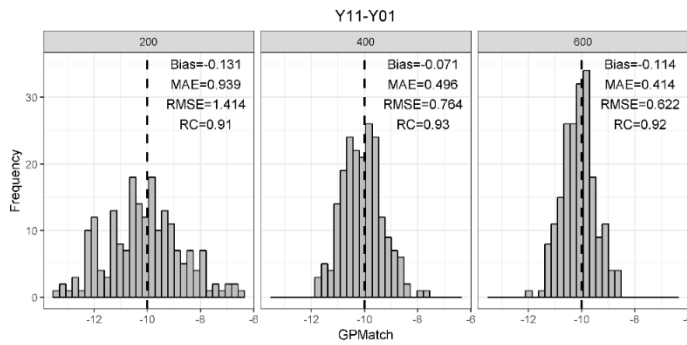
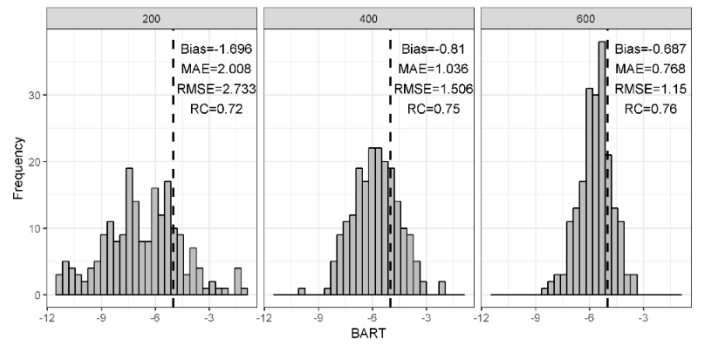
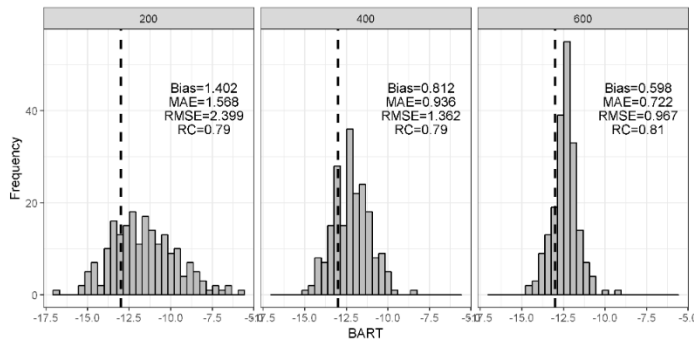
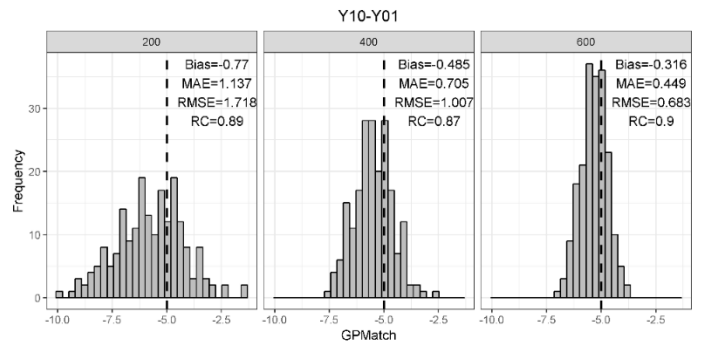
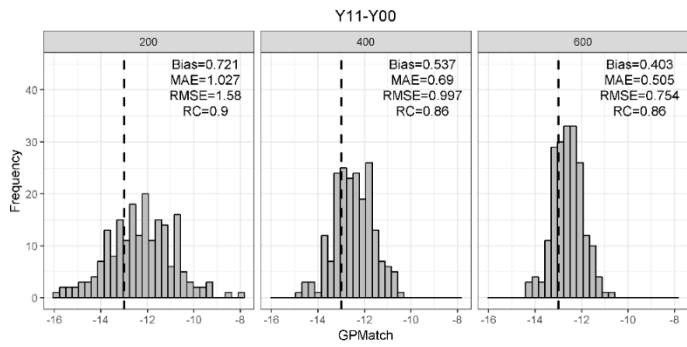


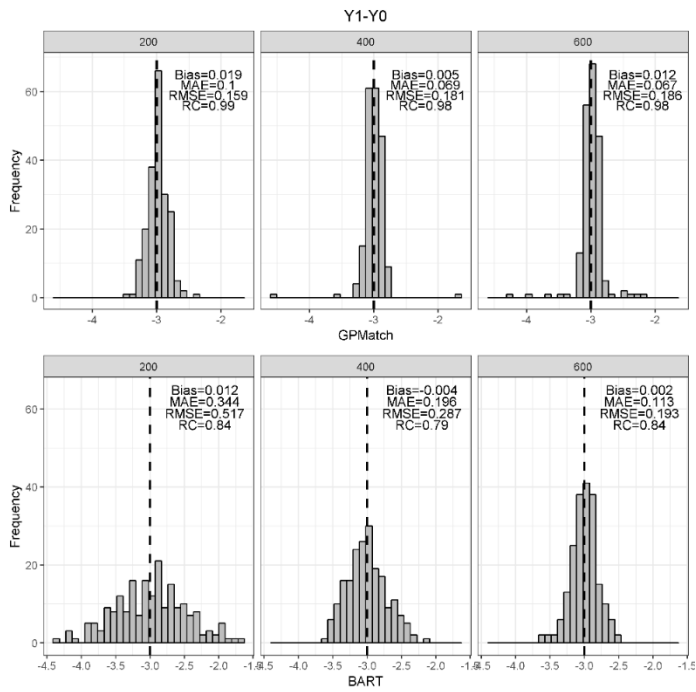
Y11-Y10



Y1-Y0







4. Heterogeneous Treatment Effect SMART Trial

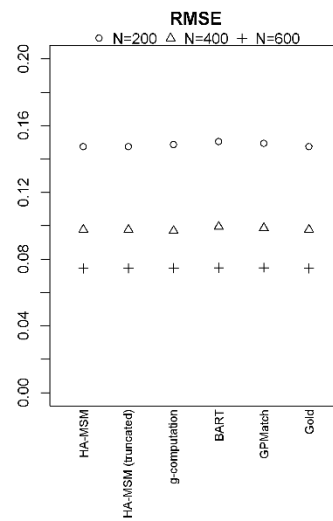
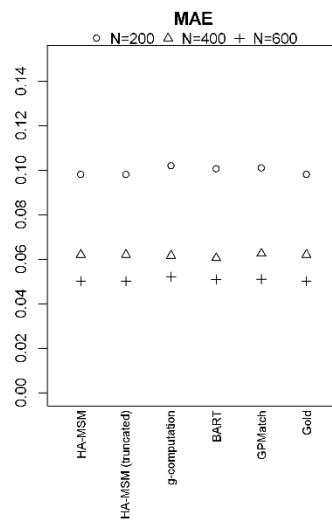
It is expected that the outcome at the 1st stage may modify the effect of the next stage treatment effect. Here, we consider a simple additive interaction effect: s

$$X \sim \text{Bernoulli}(0.4), A_0 \sim \text{Bernoulli}(0.5), L_1 \sim N(0,1)$$

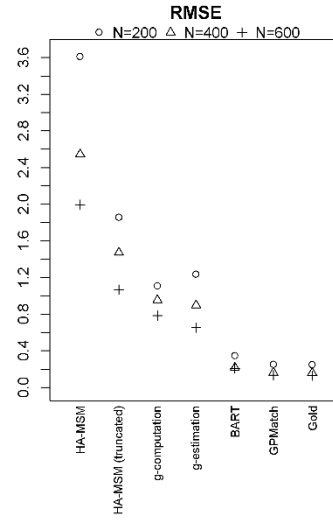
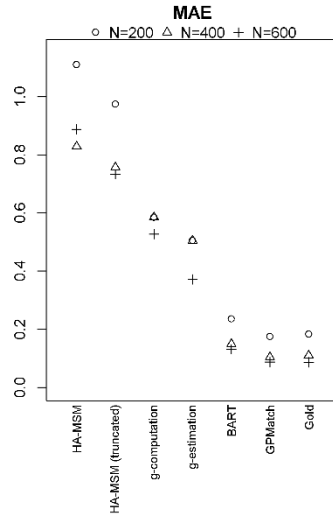
$$A_1 | L_1, A_0, X \sim \text{Bernoulli}(\text{expit}(0.2 - 0.2A_0 + L_1^{1/3}))$$

$$Y(A_0, A_1, L_1) | X \sim N(-2 + 2.5A_0 + 3.5A_1 + 0.5A_0A_1 - 3 \exp(-L_1) + A_1L_1, sd = 1)$$

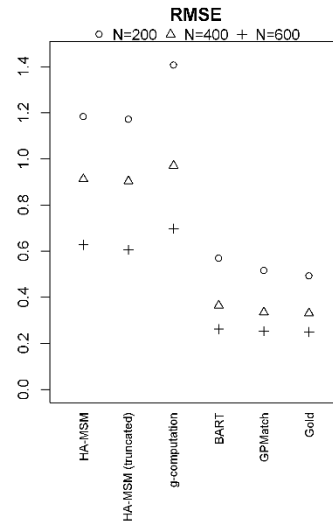
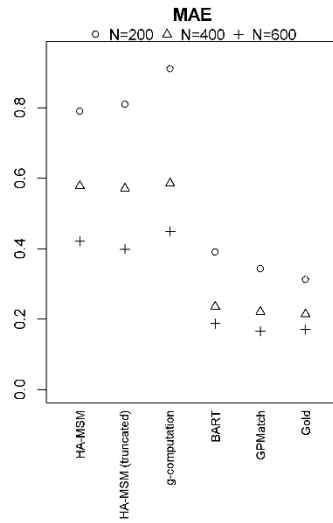
Y1-Y0



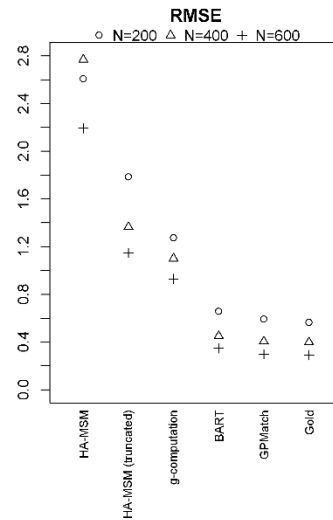
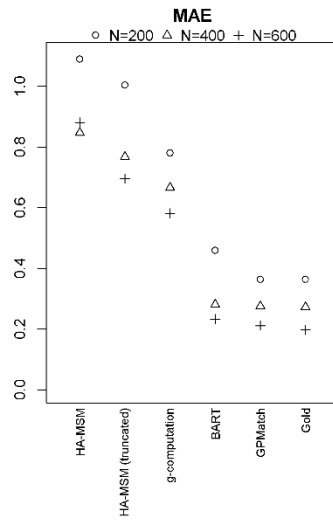
Y01-Y00



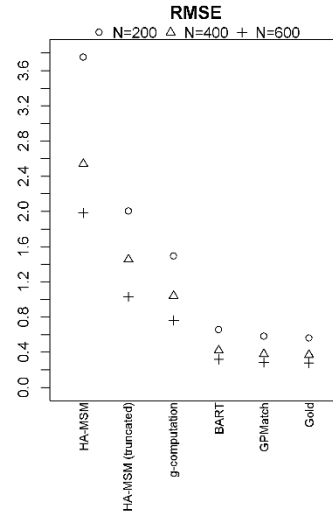
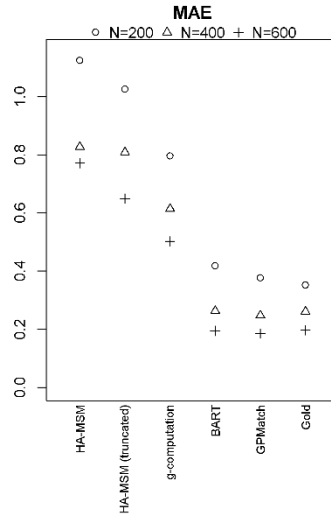
Y10-Y00



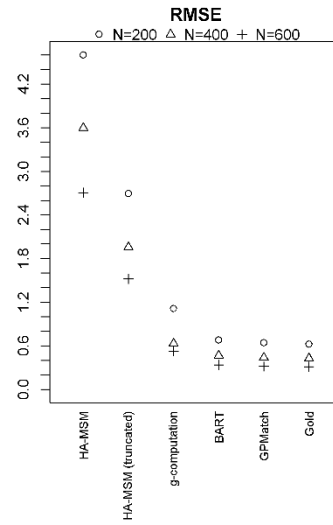
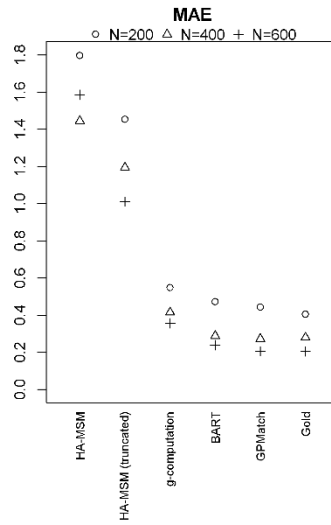
Y11-Y00



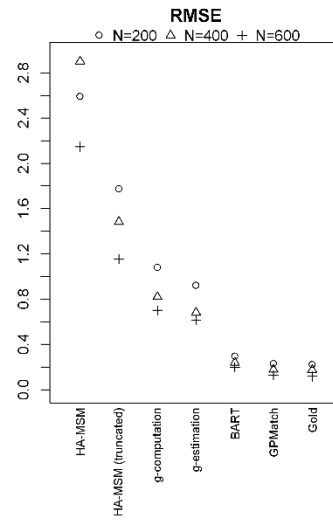
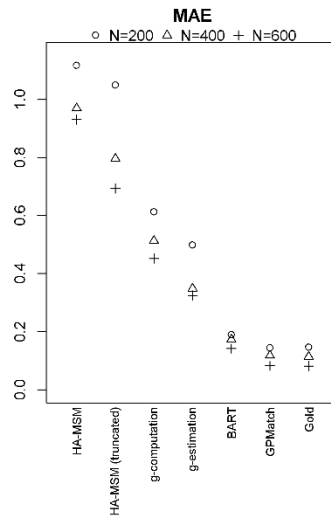
Y10-Y01

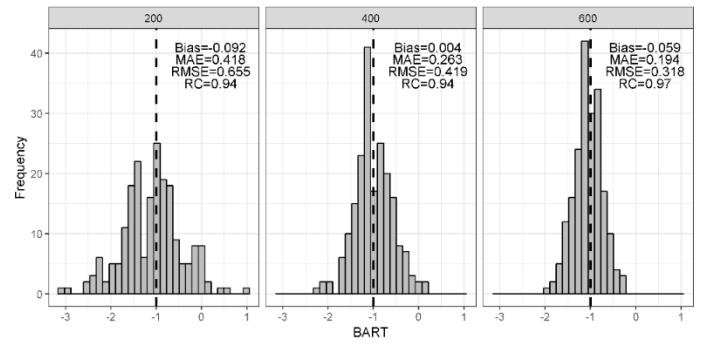
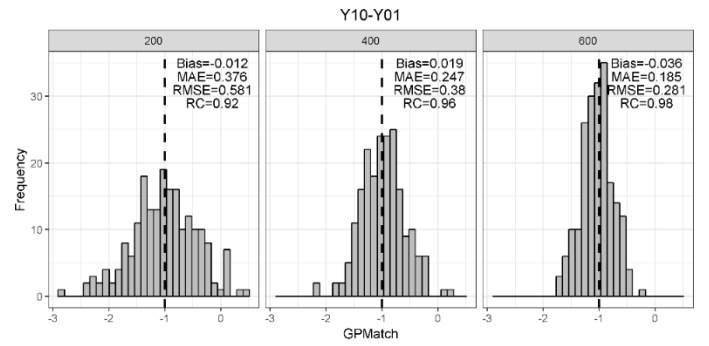
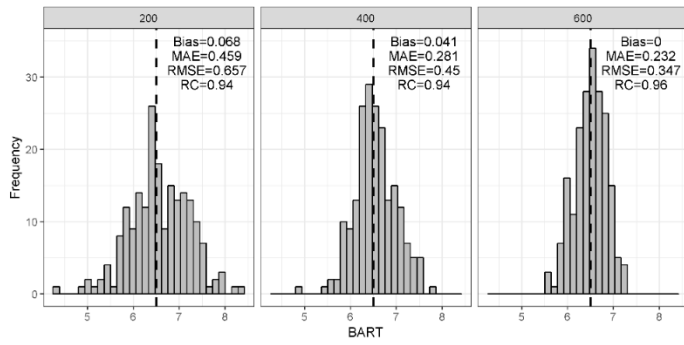
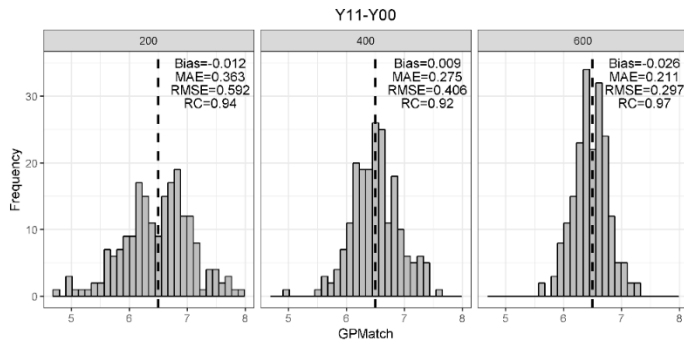
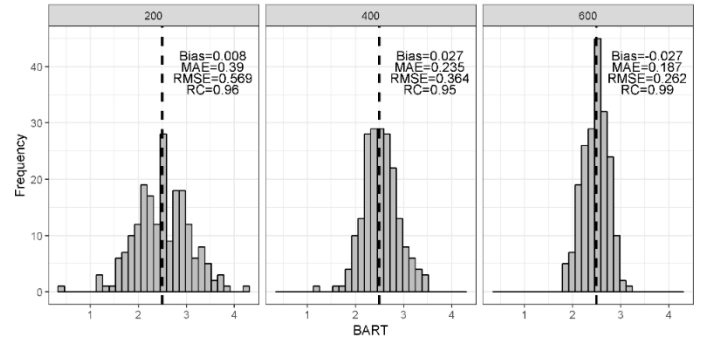
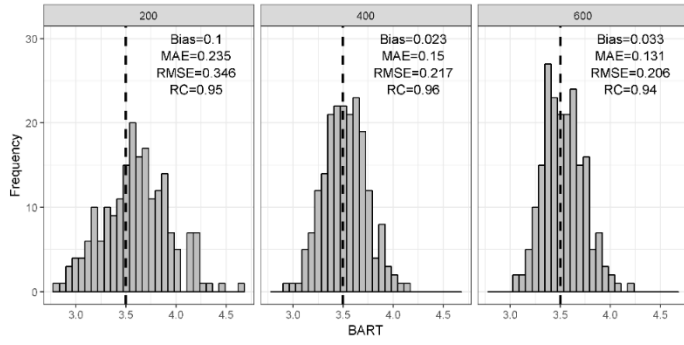
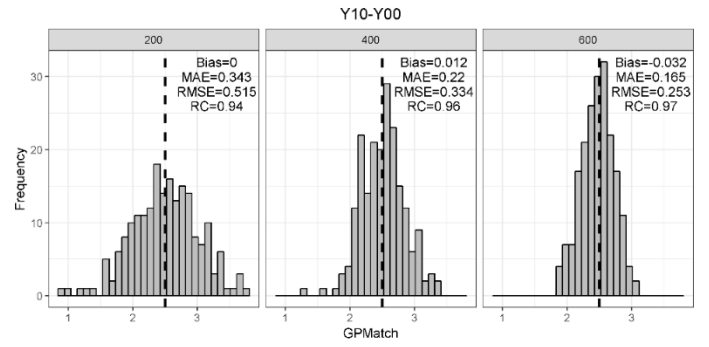
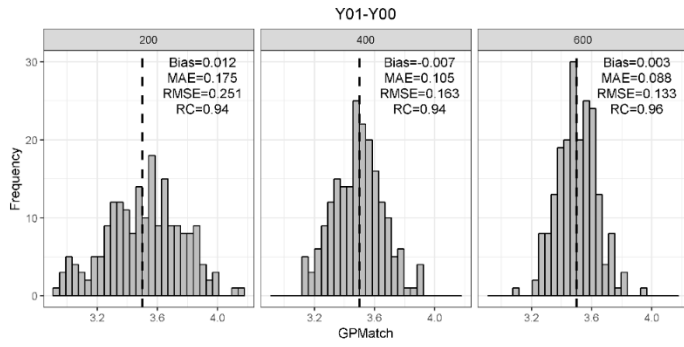


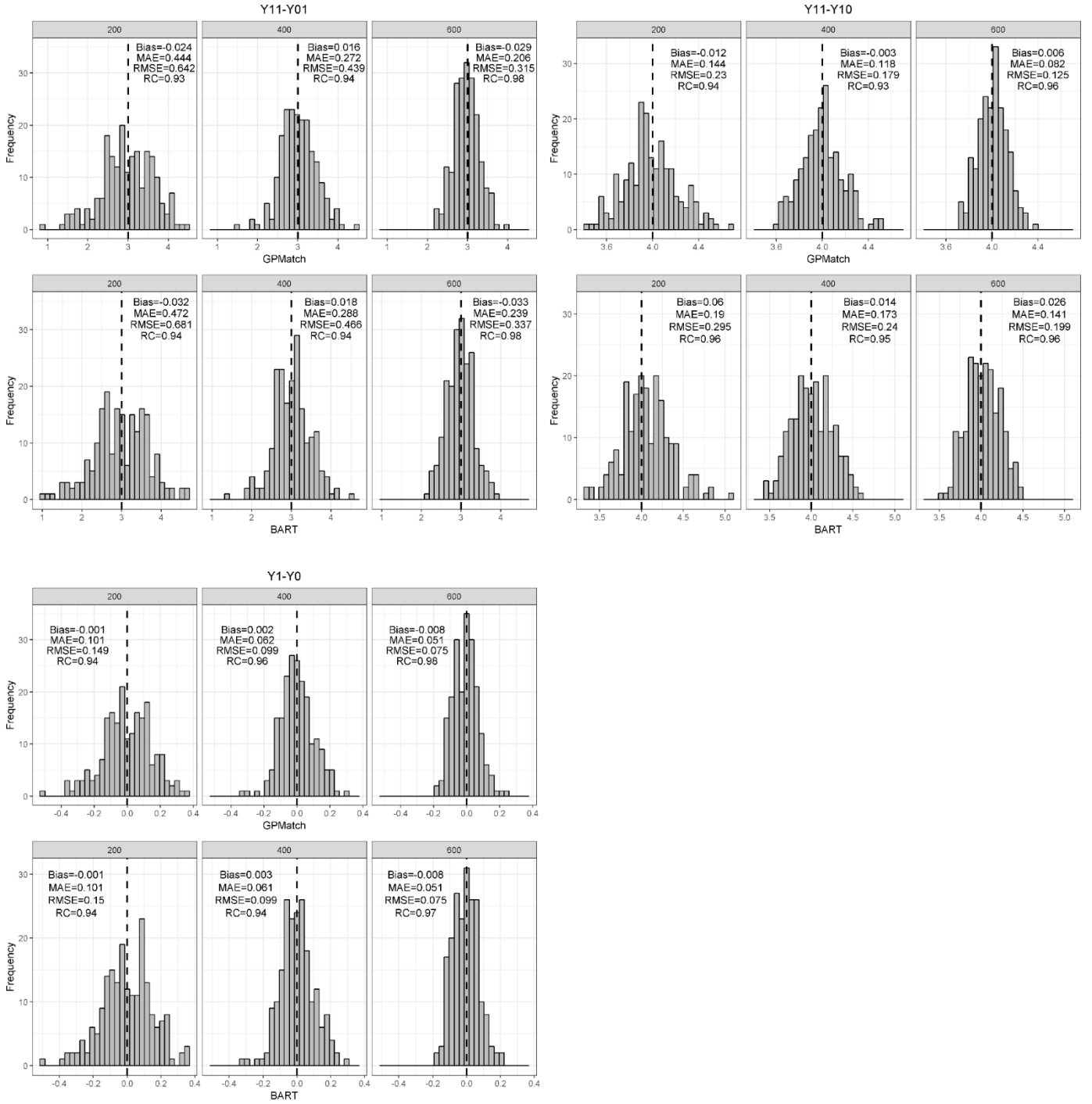
Y11-Y01



Y11-Y10







5. Observational Study Adaptive Treatment Subgroup Treatment Effect

This simulation implemented a modified simulation design setting used in Schulte's et. al. (2017). It considered a 3-level categorical baseline covariates $X = -5, 0, 5$, with multinomial distribution, $X \sim \text{Multinomial}\left(\frac{1}{3}, \frac{1}{3}, \frac{1}{3}\right)$. The causal treatment effect at both stages varies by the baseline covariates.

$$A_0 \sim \text{Bernoulli}(\text{expit}(0.3 - 0.05X))$$

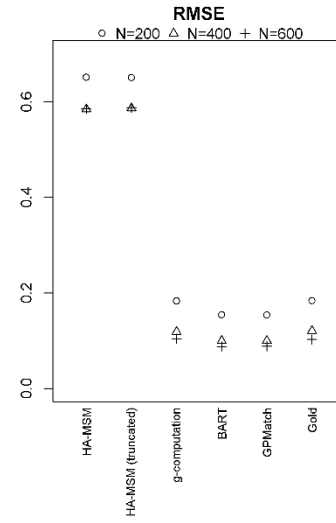
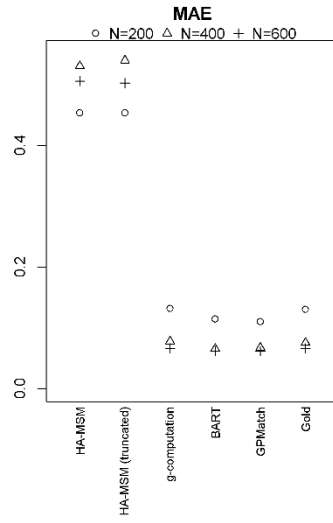
$$L_1(a_0) \sim N(0.75X - 0.75a_0 - 0.25a_0X, 1)$$

$$L_1 = A_0L_1(1) + (1 - A_0)L_1(0)$$

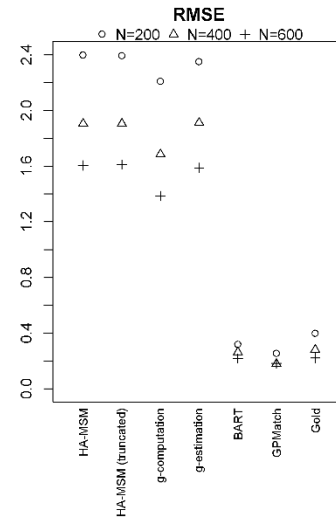
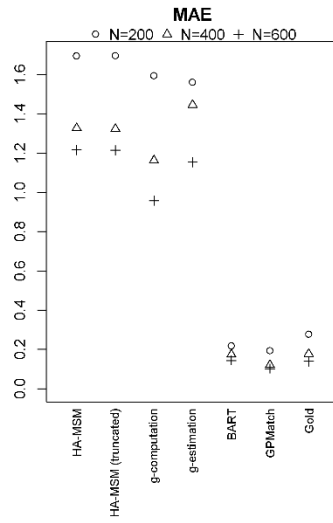
$$A_1 \sim \text{Bernoulli}(\text{expit}(0.05X + 0.2A_0 - 0.05L_1 - 0.1L_1 * A_0 - 0.01L_1^2))$$

$$Y(a_0, a_1) | L_1(a_0) \sim N(3 + 0.5a_0 + 0.4a_0X - L_1(a_0) - L_1(a_0)^2 + 2a_1 - a_0a_1 + a_1L_1(a_0), 1)$$

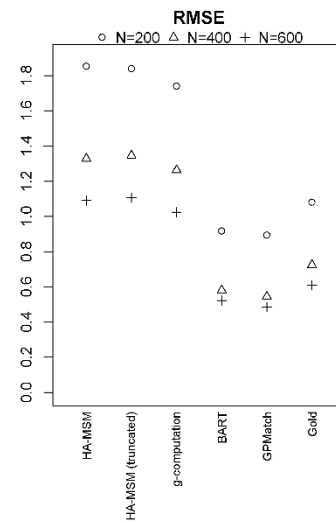
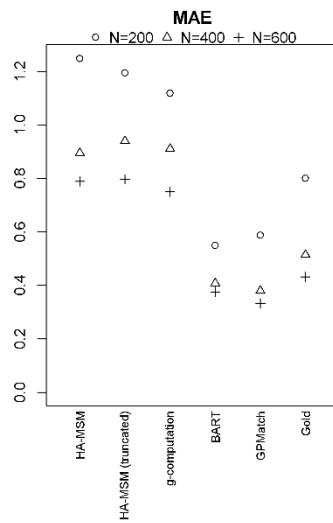
Y1-Y0



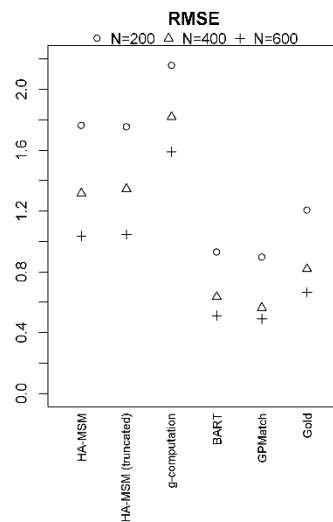
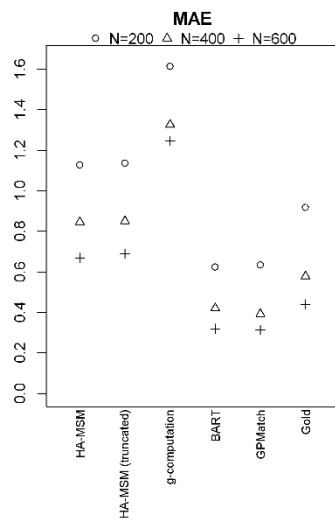
Y01-Y00



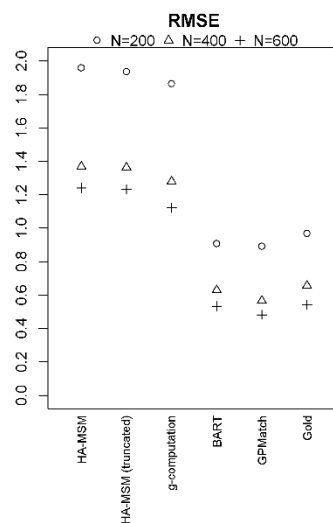
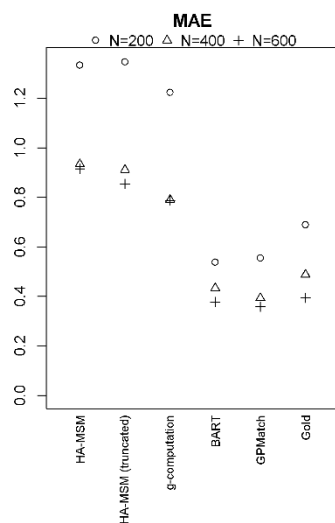
Y10-Y00



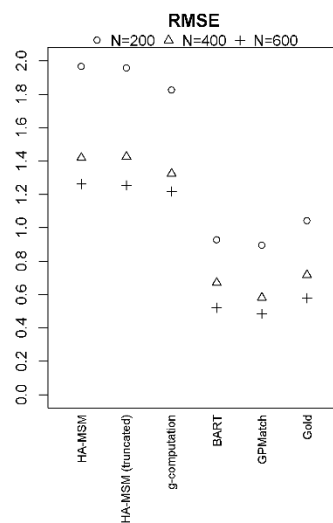
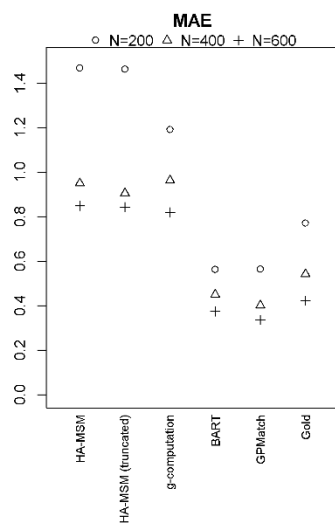
Y11-Y00

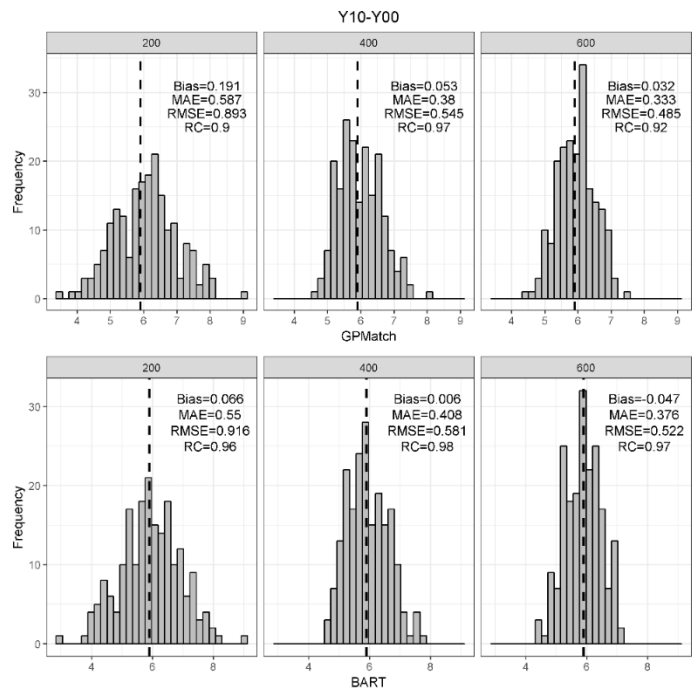
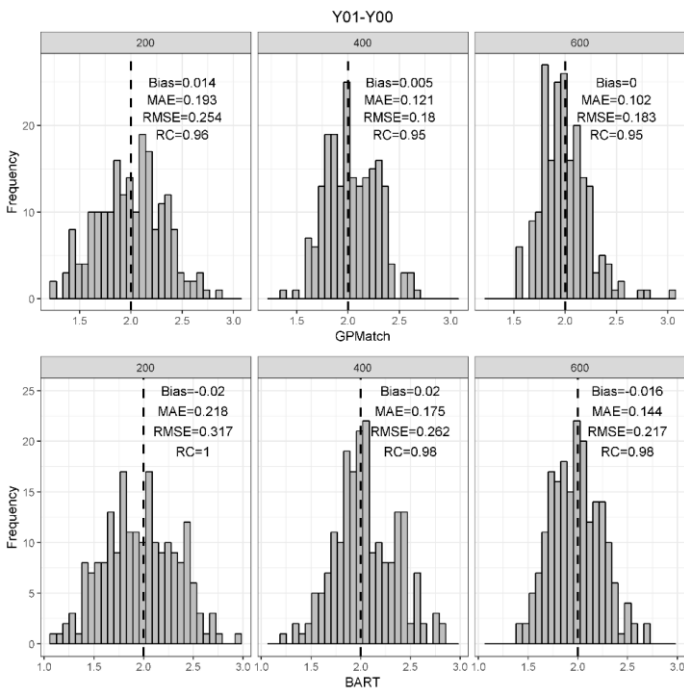
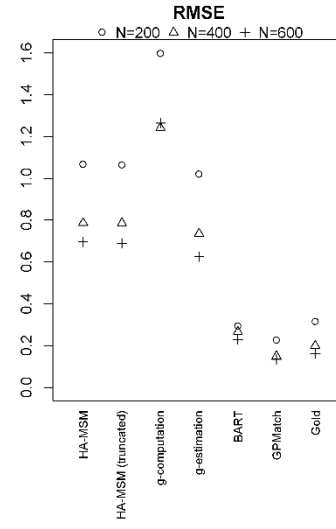
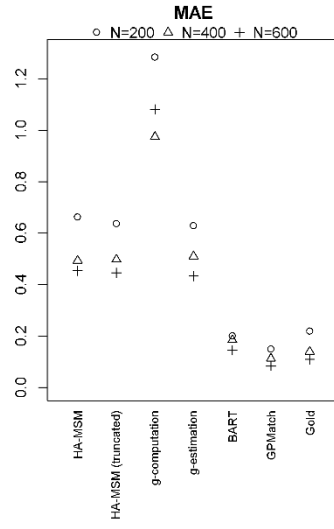


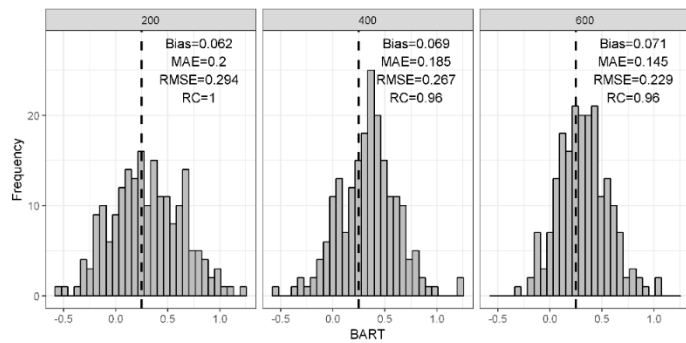
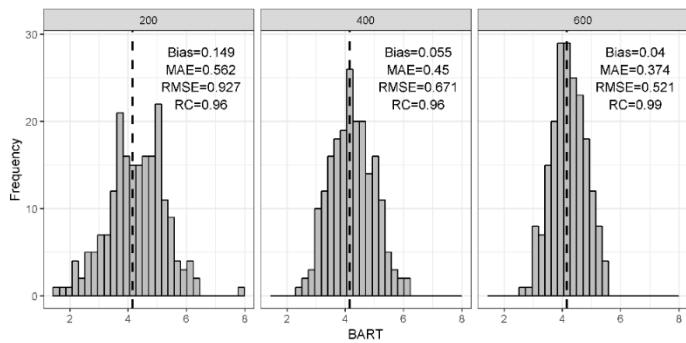
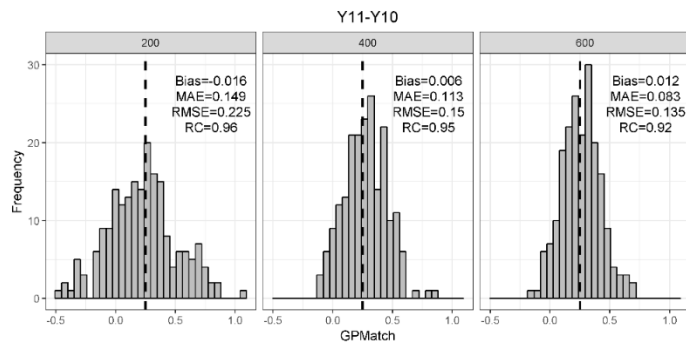
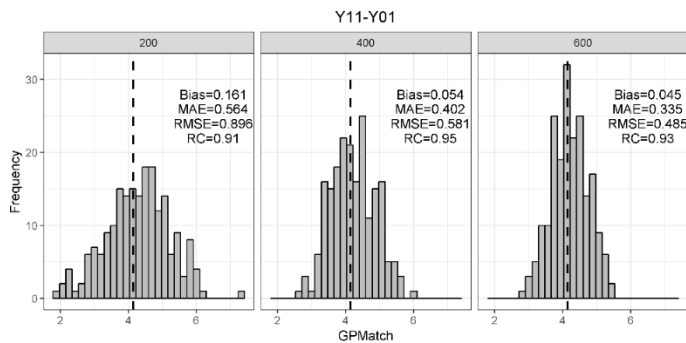
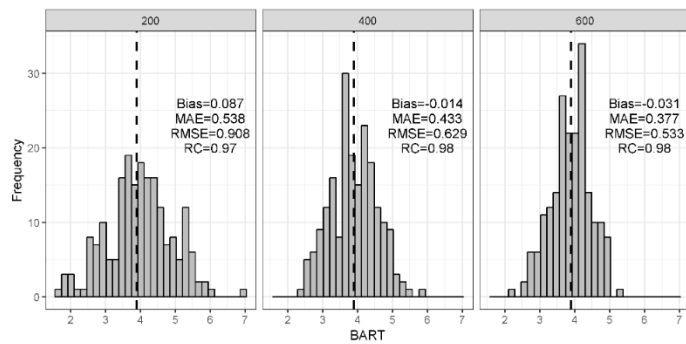
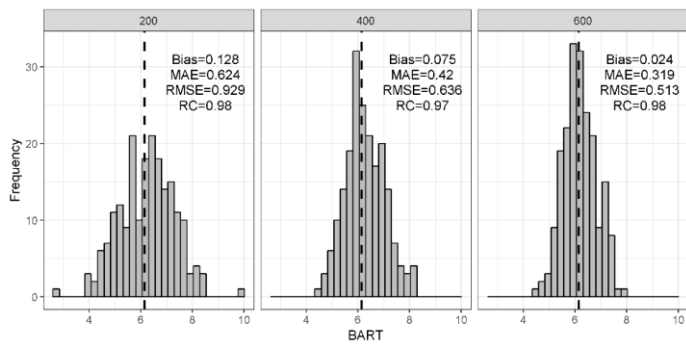
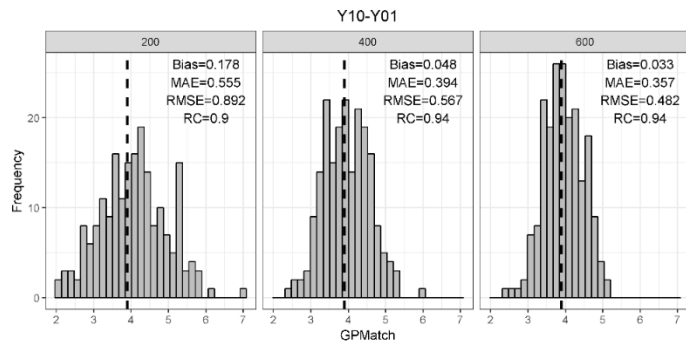
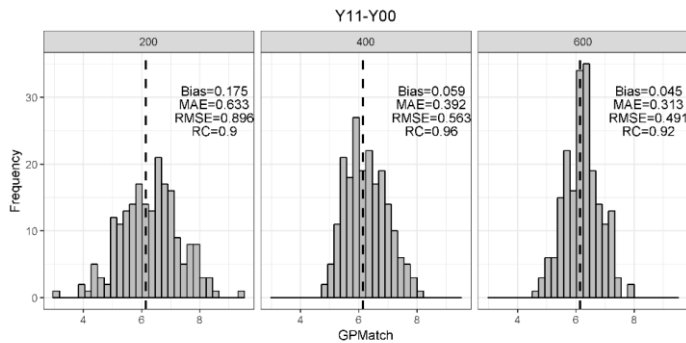
Y10-Y01



Y11-Y01







Y1-Y0

