

1 *Background*

1.1 Randomization in clinical trials

Research to identify effective and/or efficacious interventions requires balance between scientific and logistic constraints. Randomization in clinical trials allows one to infer causation from associations in the presence of an appropriate experimental design, appreciating the limitations in identifying true causal relationships. Complete randomization also ensures all variables, particularly those predictive of the outcome measurement (referred to as prognostic factors) have balanced distributions across groups, on average. However, the likelihood of imbalance increases as the trial sample size decreases or the number of measured prognostic variables increases.

Especially in small studies, at any given point in the randomization process there could be a substantial imbalance in the number of patients assigned to each group. Chance imbalance in important prognostic factors may be seen as impacting the credibility of observed treatment effect estimates. For this reason, restricted randomization techniques are often used to guarantee the sequential and overall imbalance in the number of participants in each group is controlled. We introduce restricted randomization and discuss their extension to control imbalance in prognostic factors by means of stratification or covariate adaptive randomization.

1.2 Restricted randomization

Blocked randomization is a widely accepted restricted randomization method that ensures current and overall imbalance in treatment assignments are controlled. Sequential balance is achieved by specifying a block size for which the sequence of (usually equal numbers of) treatment assignments is permuted and assigned to patients as they are enrolled. However, blocked randomization does not by itself guarantee overall balance in known prognostic variables of interest. For this reason, blocking is

often combined with stratification to make study groups comparable with regard to specified stratifying factors.

Stratified randomization is a procedure that separates the recruitment population into smaller subgroups (strata) where randomization, either simple or blocked, is performed. This property can be useful in multi-center trials, for instance, where it is of interest to account for between-center variability in patient outcomes due to unmeasured or unimportant factors *a priori*. While the randomization ratio is guaranteed to hold within pre-specified blocks of enrolled subjects, in small trials with many stratification factors one cannot assure accrued patients will fill the block for each subgroup, and randomization within strata alone will not ensure balance.

1.3 Dynamic (adaptive) randomization

Stratified block randomization is considered a static randomization method, as the probability of treatment assignment is not conditional on information on patients already enrolled. In contrast, adaptive (or dynamic) randomization approaches control imbalance by dynamically altering the randomization probability based on accrued patient information. In this thesis we consider covariate adaptive randomization procedures, which are a natural comparison to static randomization strategies intended to control imbalance of baseline prognostic factors across treatment groups. These procedures have been increasingly used as an alternative to stratified block randomization, particularly in small scale clinical trials with many prognostic factors.

Initial developments in covariate adaptive methods aimed to reduce the probability of undesirable, albeit unlikely, allocation sequences which result in both overall treatment group imbalances and imbalances within subgroups defined by important prognostic factors. In this subsection we follow the historical development of covariate adaptive

approaches with a brief discussion of the characteristics and performance of a few selected methods.

Biased coin randomization introduced by Efron (1971) was the first randomization method to change the probability of assignment dynamically based on observed covariate values of accrued patients. Simple randomization is performed until the disparity reaches a prespecified limit, at which time the group with the least subjects is biased to have a greater probability of assignment.

Taves (1974) extended Efron's biased coin design to the context of small scale clinical trials, where it is of interest to constrain imbalance in multiple prognostic factors across treatment groups. Briefly, the method sequentially allocates incoming patients deterministically to the treatment category that minimizes the overall unweighted sum of covariate imbalance given the new assignment. The assignment is performed deterministically: assignment is randomized only when assignment to either treatment category results in the same imbalance. Pocock and Simon (1975) further generalized Taves' method to incorporate relative importance of prognostic factors by introducing weighting of covariate imbalances into the overall imbalance metric.

Signorini et. al 1993 extended earlier methods in order to induce balance both overall and within strata while avoiding investigator bias through unblinding. He proposed a tree-based method of dynamic balancing randomization (DBR) that evaluates imbalance for each prognostic factor in a nested fashion by their prespecified order of importance. The method flexibly allows for different levels of imbalance in different strata and ensures conditional balance, meaning that within each subgroup the ratio of treatment assignment is constrained within prespecified bounds. However, the method does not guarantee balanced group assignments will be achieved within each prognostic factor considered separately.

Heritier et. al (2005) modify Signorini et. al's DBR method to control imbalance

marginally within each prognostic factor. For each accrued patient, the potential imbalance for each treatment assignment is considered sequentially within each prognostic factor in decreasing order of importance. If the potential observed imbalance exceeds a prespecified threshold, assignment is performed deterministically (or forced) to the group which minimizes the imbalance. Heritier et. al suggested including non-deterministic allocation to reduce the number of forced allocations and prevent investigator unblinding.

Model-based approaches are another alternative approach to dynamic randomization, where the probability of treatment assignment is chosen to minimize the variance of the estimated treatment effect. Model-based methods can flexibly incorporate continuous prognostic factors without the need to dichotomize into groups, and can include interaction terms and balance prognostic factors even when the number of variables is large. Aickin (1998, 2001, 2009) proposed a model-based approach to covariate adaptive randomization, where a subjects' treatment assignment is based on maximizing the log-likelihood of the model.

1.4 Adjusting for prognostic factors in the analysis model

Statistical adjustment is another approach to addressing prognostic factors that may confound the relationship between an intervention (the predictor of interest) and the outcome measure. Oftentimes it is of interest to measure and adjust for known variables predictive of the outcome measurement in the analysis model. It may be scientifically meaningful to provide estimates for known confounders or if the effect may differ within subgroups. Statistically, adjustment can potentially reduce bias from confounding and increase efficiency. Statistical adjustment accounts for, but

does not control, imbalance in known prognostic factors predictive of the outcome measurement.

1.5 Analysis considerations under alternative randomization schemes

Analysis of trials using a covariate adaptive allocation (CAA) scheme must account for the randomization scheme to recover the precision gains conferred by inducing more balanced treatment groups with respect to chosen balancing factors. To obtain the correct variance term and significance level for the test statistic, one must consider all possible sequences of assignments which could have been made in repeated trials assuming no group differences in mean response. In most cases, ignoring the randomization procedure and using standard regression methods that implicitly assume complete randomization lead to larger variance estimates and conservative inference. Since CAA modifies the randomization scheme to induce similarity across treatment arms relative to within arms, the efficiency gain can be realized using a nonparametric re-randomization approach for estimating standard errors (Simon and Simon 2011). Briefly, observed values and entry order are fixed, treatment assignments are reshuffled and the test statistic computed for each permutation.

1.6 Aims

The goal of the thesis is to address in both the binary and continuous outcome setting if covariate adaptive randomization (CAR) followed by standard asymptotic tests yield valid inference, and if so, to quantify the gains in precision relative to simple randomization (SR) or stratified block randomization (SBR). We will compare

Heritier's modified DBR scheme to stratified block randomization and complete randomization, while comparing re-randomization based permutation tests to standard asymptotic tests in a simulation study. We will consider the setting of equal allocation to treatment assignment, no temporal trend (drift), binary predictors, and two outcome types (binary and continuous). Our objective is to identify any scenarios, if any, where minimization improves power relative to SBR or simple randomization. Contour plots of effect size by sample size will compare power across methods for various outcome types and conditions.

We are also interested if and when the answers to the above questions change when the effect size of prognostic factors is varied relative to the treatment effect, the baseline prevalence varies from 5% to 50% in the binary outcome setting, inference on treatment effect is performed using none (or a subset) of the prognostic variables, and when the sample size is varied. It is well known that ignoring the minimization design tends to yield conservative inference, and that adjusting for covariates used in the randomization scheme (balancing factors) recovers type I error rate to nominal significance levels (Xu, Proschan, Lee 2016). Through comparison of estimated marginal and conditional treatment effects we seek to confirm this finding. We consider different sample sizes ranging from $N=32$ to 96 to compare CAR to SBR as small scale trials are the setting in which alternative randomization methods are considered. We seek to identify the specific conditions by which CAR confers a precision advantage, if any, relative to other methods to offset the operational complexities involved in implementing an adaptive allocation procedure. Our intent is to provide guidance to clinical researchers for determining under what settings covariate adaptive allocation provides precision gains relative to competing approaches as well as which analysis method yields valid tests with the most power.

Chapter 2 will introduce the notation used throughout the thesis, and Chapter

3 will discuss the design of the simulation study in further detail. The tables of simulation results will be presented in Chapter 4 and the key observations will be discussed in Chapter 5.

1.7 Measures to evaluate aims

For each combination of randomization scheme and analysis approach, we assess validity by estimating the nominal significance level of the test under the null hypothesis. We evaluate accuracy by estimating any potential bias and the coverage probability of confidence intervals, comparing those generated with standard regression methods (Wald-type) to permutation test quantile-based confidence intervals. Average standard error estimates will also be reported for analyses using standard regression methods. We evaluate efficiency by computing mean squared error (MSE) and power as a function of the true treatment effect size.

2 *Methods*

2.1 Data generation

Simulations were conducted of a two-arm randomized clinical trial with equal allocation (1:1 treatment:control). We conducted simulations for both continuous and binary outcome and covariate types, and varied the overall trial size from 32 to 96.

The outcome measure (Y) was simulated with a marginal prevalence of 10% or 50% in the binary setting to evaluate the potential impact of low numbers of observed outcomes on inference. Continuous outcomes were simulated as normally distributed with constant variance, with mean as a linear combination of the treatment assignment (Z), pre-specified risk factors (X), and observed entry time (T).

Binary risk factors were simulated such that their marginal prevalence was either 25% or 50%. Continuous risk factors (X) were generated under a standard normal distribution. The risk factors are modeled as independent. The effect sizes for treatment assignment (Z) and prognostic variables (X) were separately varied from none, low, medium, and high. Balancing factors refer to risk factors used in adaptive allocation procedures, for which it is desired to have comparability either within or between treatment groups. The exact type of balance desired informs the choice of imbalance metric minimized at each sequential allocation step. For instance, it may be of interest to ensure within-strata subgroups have approximately proportional treatment and control assignments (conditional balance), or that treatment groups are otherwise comparable with respect to pre-specified balancing factors (marginal balance).

Observed patient entry times occurred following a uniform distribution. In subsequent re-randomization analysis, patient entry order is considered fixed (see Section 2aiv on re-randomization tests). Temporal trends in outcome prevalence over the course of a study (drift) were modeled by varying the entry time effect size from none, mild,

to severe. For the binary response setting under severe drift, for instance, the drift effect size was chosen such that marginal outcome prevalence varies three-fold over the study period.

2.2 Allocation procedures

For each simulated set of observed entry times and prognostic factors, treatment group assignments were determined using three allocation procedures: complete randomization, stratified permuted block randomization with fixed block sizes equal to overall trial size divided by number of strata (defined by all combinations of balancing factor levels), and an adapted form of covariate adaptive randomization proposed by Heritier et. al (2005).

For the covariate-adaptive randomization procedure, the maximum imbalance of treatment to control assignments (overall and within strata defined by each balancing factor level, considered separately) was set to 2. The allocation biasing probability, or the probability of assigning patient to treatment minimizing the imbalance measure when prospective imbalance meets or exceeds a prespecified threshold, was chosen as 0.7 to minimize the effect of non-deterministic and forced allocations on inference.

2.3 Varied conditions

The following table describes the conditions varied in the binary outcome setting. Note: in the continuous outcome setting, the effect sizes are modified to represent comparable differences in means to the given odds ratios.

2.4 Analysis approaches

For each allocation procedure we estimated the treatment effect, adjusted and unadjusted for balancing factors. To evaluate power, coverage, and type I error control, we report the associated linear and logistic regression model-based p-values, standard errors and Wald-type confidence intervals, based on a two-sided type I error threshold (alpha) of 0.05. For balancing purposes, continuous balancing factors were first dichotomized by their population median, and later parameterized as continuous in the adjusted analysis.

The simulation model is of the form

The adjusted regression model is

The unadjusted model

To compare the bias and power based on re-randomization analysis to that based on standard regression techniques, we compute power, coverage, and level and conducted re-randomization based inference for each simulated trial following covariate adaptive randomization. Re-randomization is a permutation-based method for estimating uncertainty and follows from the generally accepted sentiment to ‘analyze as you randomize’. The approach considers the outcomes (Y), balancing factors (X), and observed entry time (T) as fixed and repeats the allocation procedure multiple times, each generating a new sequence of treatment assignments (. Regression estimates are computed under each re-randomized treatment allocation sequence, and re-randomization based 95% confidence intervals are generated using the 2.5th and 97.5th quantile of the re-randomization-based treatment effect estimates. Re-randomization based p-values are estimated using the observed proportion of re-randomized allocation sequences yielding treatment effect estimates as or more extreme than the observed treatment effect.

Each simulation model configuration was simulated 10,000 trials, for which the re-randomization procedure was repeated 500 times.

3 *Simulation*

3.1 Batch 1: Binary Outcome, Binary Predictors

Table 3.1: Batch 1 (Binary Y, Binary X): Power

n	Pr(Y)	Pr(X)	bZ	bX	Model-based				Rerandomization		
					CR		SBR		CAA		CAA
					adj	unadj	adj	unadj	adj	unadj	adj
32	0.1	0.25	1.0	1.1	0.009	0.001	0.006	0.000	0.007	0.000	0.075
32	0.1	0.25	1.0	3.0	0.015	0.001	0.017	0.000	0.018	0.001	0.071
32	0.1	0.25	1.1	1.1	0.009	0.001	0.007	0.000	0.008	0.000	0.077
32	0.1	0.25	1.1	3.0	0.016	0.001	0.017	0.000	0.020	0.001	0.070
32	0.1	0.25	3.0	1.1	0.015	0.004	0.012	0.003	0.013	0.003	0.147
32	0.1	0.25	3.0	3.0	0.024	0.007	0.025	0.004	0.026	0.007	0.157
32	0.1	0.50	1.0	1.1	0.009	0.000	0.008	0.000	0.005	0.000	0.078
32	0.1	0.50	1.0	3.0	0.018	0.001	0.022	0.001	0.020	0.001	0.070
32	0.1	0.50	1.1	1.1	0.009	0.001	0.007	0.000	0.004	0.000	0.079
32	0.1	0.50	1.1	3.0	0.019	0.002	0.021	0.000	0.022	0.001	0.071
32	0.1	0.50	3.0	1.1	0.015	0.004	0.009	0.002	0.013	0.004	0.149
32	0.1	0.50	3.0	3.0	0.042	0.007	0.040	0.003	0.045	0.006	0.165
32	0.5	0.25	1.0	1.1	0.028	0.029	0.031	0.026	0.028	0.025	0.057
32	0.5	0.25	1.0	3.0	0.019	0.023	0.022	0.017	0.025	0.022	0.056
32	0.5	0.25	1.1	1.1	0.025	0.027	0.027	0.022	0.033	0.029	0.063
32	0.5	0.25	1.1	3.0	0.023	0.025	0.024	0.017	0.026	0.022	0.059
32	0.5	0.25	3.0	1.1	0.210	0.230	0.232	0.230	0.222	0.219	0.326
32	0.5	0.25	3.0	3.0	0.172	0.192	0.197	0.181	0.198	0.182	0.302
32	0.5	0.50	1.0	1.1	0.026	0.029	0.026	0.025	0.026	0.025	0.062
32	0.5	0.50	1.0	3.0	0.022	0.025	0.028	0.016	0.024	0.019	0.059
32	0.5	0.50	1.1	1.1	0.029	0.030	0.024	0.023	0.024	0.023	0.064
32	0.5	0.50	1.1	3.0	0.027	0.031	0.028	0.018	0.028	0.022	0.061
32	0.5	0.50	3.0	1.1	0.202	0.226	0.223	0.223	0.223	0.228	0.327
32	0.5	0.50	3.0	3.0	0.161	0.177	0.190	0.164	0.180	0.170	0.300
96	0.1	0.25	1.0	1.1	0.026	0.018	0.024	0.019	0.026	0.018	0.058
96	0.1	0.25	1.0	3.0	0.038	0.026	0.041	0.026	0.036	0.019	0.051
96	0.1	0.25	1.1	1.1	0.025	0.019	0.027	0.020	0.028	0.018	0.063
96	0.1	0.25	1.1	3.0	0.038	0.027	0.040	0.025	0.039	0.022	0.055
96	0.1	0.25	3.0	1.1	0.226	0.210	0.213	0.205	0.224	0.207	0.358
96	0.1	0.25	3.0	3.0	0.270	0.245	0.274	0.241	0.278	0.242	0.376
96	0.1	0.50	1.0	1.1	0.024	0.018	0.025	0.017	0.026	0.018	0.060

96	0.1	0.50	1.0	3.0	0.045	0.024	0.044	0.021	0.048	0.026	0.061
96	0.1	0.50	1.1	1.1	0.025	0.019	0.023	0.018	0.027	0.019	0.061
96	0.1	0.50	1.1	3.0	0.047	0.026	0.045	0.021	0.049	0.025	0.060
96	0.1	0.50	3.0	1.1	0.217	0.212	0.219	0.207	0.232	0.218	0.363
96	0.1	0.50	3.0	3.0	0.308	0.267	0.328	0.277	0.318	0.267	0.394
96	0.5	0.25	1.0	1.1	0.043	0.045	0.044	0.048	0.038	0.045	0.050
96	0.5	0.25	1.0	3.0	0.046	0.047	0.045	0.041	0.043	0.041	0.055
96	0.5	0.25	1.1	1.1	0.046	0.049	0.049	0.052	0.046	0.052	0.057
96	0.5	0.25	1.1	3.0	0.050	0.051	0.051	0.048	0.048	0.047	0.060
96	0.5	0.25	3.0	1.1	0.725	0.744	0.730	0.745	0.741	0.764	0.752
96	0.5	0.25	3.0	3.0	0.680	0.649	0.691	0.675	0.683	0.672	0.704
96	0.5	0.50	1.0	1.1	0.044	0.047	0.045	0.050	0.048	0.053	0.059
96	0.5	0.50	1.0	3.0	0.042	0.048	0.042	0.036	0.046	0.044	0.058
96	0.5	0.50	1.1	1.1	0.045	0.047	0.049	0.054	0.050	0.056	0.059
96	0.5	0.50	1.1	3.0	0.046	0.048	0.047	0.042	0.046	0.040	0.057
96	0.5	0.50	3.0	1.1	0.725	0.741	0.740	0.757	0.739	0.758	0.752
96	0.5	0.50	3.0	3.0	0.661	0.629	0.676	0.647	0.669	0.648	0.694

Table 3.2: Batch 1 (Binary Y, Binary X): Median bias

n	Pr(Y)	Pr(X)	bZ	bX	Model-based				Rerandomization	
					CR		SBR		CAA	
					adj	unadj	adj	unadj	adj	unadj
32	0.1	0.25	1.0	1.1	0.000	0.000	0.000	0.000	0.000	0.000
32	0.1	0.25	1.0	3.0	0.000	0.000	0.000	0.000	0.000	0.000
32	0.1	0.25	1.1	1.1	-0.019	-0.044	-0.095	-0.095	-0.065	-0.095
32	0.1	0.25	1.1	3.0	-0.007	0.038	-0.045	-0.095	-0.028	-0.095
32	0.1	0.25	3.0	1.1	0.297	0.167	0.196	0.143	0.237	0.143
32	0.1	0.25	3.0	3.0	0.316	0.065	0.227	0.000	0.282	0.000
32	0.1	0.50	1.0	1.1	0.000	0.000	0.000	0.000	0.000	0.000
32	0.1	0.50	1.0	3.0	0.000	0.000	0.000	0.000	0.000	0.000
32	0.1	0.50	1.1	1.1	-0.013	-0.065	-0.095	-0.095	-0.079	-0.095
32	0.1	0.50	1.1	3.0	0.028	0.022	-0.011	-0.095	-0.031	-0.095
32	0.1	0.50	3.0	1.1	0.289	0.143	0.173	0.065	0.284	0.143
32	0.1	0.50	3.0	3.0	0.283	0.065	0.222	0.059	0.229	0.059
32	0.5	0.25	1.0	1.1	0.012	0.000	0.000	0.000	0.000	0.000
32	0.5	0.25	1.0	3.0	0.001	0.000	0.000	0.000	-0.003	0.000
32	0.5	0.25	1.1	1.1	0.021	-0.008	0.008	-0.047	0.011	-0.031
32	0.5	0.25	1.1	3.0	0.030	-0.026	0.009	-0.047	-0.006	-0.047
32	0.5	0.25	3.0	1.1	0.131	0.031	0.145	0.031	0.128	-0.011
32	0.5	0.25	3.0	3.0	0.176	-0.049	0.117	-0.059	0.148	-0.059
32	0.5	0.50	1.0	1.1	-0.007	0.000	-0.008	0.000	0.012	0.000
32	0.5	0.50	1.0	3.0	-0.003	0.000	-0.014	0.000	0.000	0.000
32	0.5	0.50	1.1	1.1	-0.002	-0.031	-0.014	-0.047	0.012	-0.047
32	0.5	0.50	1.1	3.0	0.006	-0.047	-0.004	-0.047	-0.010	-0.080
32	0.5	0.50	3.0	1.1	0.136	0.031	0.168	0.031	0.133	0.000
32	0.5	0.50	3.0	3.0	0.144	-0.087	0.153	-0.077	0.149	-0.077
96	0.1	0.25	1.0	1.1	0.004	0.000	0.001	0.000	0.002	0.000
96	0.1	0.25	1.0	3.0	0.001	0.000	-0.002	0.000	-0.005	0.000
96	0.1	0.25	1.1	1.1	0.009	0.002	-0.004	-0.004	-0.007	-0.013
96	0.1	0.25	1.1	3.0	-0.001	-0.004	-0.001	-0.002	0.006	-0.013
96	0.1	0.25	3.0	1.1	0.081	0.047	0.084	0.047	0.077	0.047
96	0.1	0.25	3.0	3.0	0.065	-0.045	0.071	-0.047	0.062	-0.047
96	0.1	0.50	1.0	1.1	0.007	0.000	0.005	0.000	0.000	0.000
96	0.1	0.50	1.0	3.0	-0.001	0.000	0.018	0.000	0.001	0.000
96	0.1	0.50	1.1	1.1	0.009	0.000	0.002	-0.002	-0.009	-0.035
96	0.1	0.50	1.1	3.0	0.006	-0.013	0.017	0.002	0.011	0.000

96	0.1	0.50	3.0	1.1	0.085	0.054	0.070	0.047	0.093	0.054	0.093
96	0.1	0.50	3.0	3.0	0.062	-0.037	0.065	-0.036	0.077	-0.036	0.077
96	0.5	0.25	1.0	1.1	0.013	0.007	0.002	0.000	0.001	0.000	0.001
96	0.5	0.25	1.0	3.0	0.016	0.009	0.000	0.000	0.007	0.000	0.007
96	0.5	0.25	1.1	1.1	0.006	-0.001	-0.004	-0.011	-0.001	-0.011	-0.001
96	0.5	0.25	1.1	3.0	0.021	0.007	-0.002	-0.012	0.015	-0.010	0.015
96	0.5	0.25	3.0	1.1	0.039	0.013	0.037	0.013	0.038	0.013	0.038
96	0.5	0.25	3.0	3.0	0.046	-0.084	0.039	-0.078	0.036	-0.078	0.036
96	0.5	0.50	1.0	1.1	-0.008	-0.005	-0.005	0.000	0.005	0.000	0.005
96	0.5	0.50	1.0	3.0	-0.007	0.000	-0.008	0.000	0.005	0.000	0.005
96	0.5	0.50	1.1	1.1	-0.002	-0.008	-0.001	-0.009	0.001	-0.008	0.001
96	0.5	0.50	1.1	3.0	0.013	-0.007	0.011	-0.012	-0.002	-0.012	-0.002
96	0.5	0.50	3.0	1.1	0.042	0.013	0.041	0.017	0.037	0.013	0.037
96	0.5	0.50	3.0	3.0	0.037	-0.112	0.032	-0.143	0.041	-0.136	0.041

Table 3.3: Batch 1 (Binary Y, Binary X): Coverage probability

n	Pr(Y)	Pr(X)	bZ	bX	Model-based					
					CR		SBR		CAA	
					adj	unadj	adj	unadj	adj	unadj
32	0.1	0.25	1.0	1.1	0.989	0.999	0.993	1.000	0.991	0.999
32	0.1	0.25	1.0	3.0	0.983	0.998	0.979	0.999	0.979	0.999
32	0.1	0.25	1.1	1.1	0.989	0.999	0.992	1.000	0.990	0.999
32	0.1	0.25	1.1	3.0	0.982	0.998	0.979	0.999	0.978	0.999
32	0.1	0.25	3.0	1.1	0.958	0.968	0.962	0.971	0.957	0.968
32	0.1	0.25	3.0	3.0	0.969	0.979	0.959	0.975	0.957	0.975
32	0.1	0.50	1.0	1.1	0.988	0.999	0.991	0.999	0.993	0.998
32	0.1	0.50	1.0	3.0	0.979	0.998	0.974	0.998	0.975	0.998
32	0.1	0.50	1.1	1.1	0.988	0.999	0.992	0.999	0.992	0.999
32	0.1	0.50	1.1	3.0	0.977	0.997	0.975	0.999	0.974	0.998
32	0.1	0.50	3.0	1.1	0.954	0.966	0.959	0.967	0.954	0.967
32	0.1	0.50	3.0	3.0	0.956	0.977	0.960	0.977	0.958	0.976
32	0.5	0.25	1.0	1.1	0.963	0.954	0.958	0.948	0.964	0.956
32	0.5	0.25	1.0	3.0	0.973	0.960	0.967	0.959	0.965	0.957
32	0.5	0.25	1.1	1.1	0.965	0.964	0.966	0.968	0.959	0.961
32	0.5	0.25	1.1	3.0	0.969	0.967	0.966	0.971	0.965	0.967
32	0.5	0.25	3.0	1.1	0.967	0.962	0.966	0.961	0.967	0.962
32	0.5	0.25	3.0	3.0	0.975	0.967	0.978	0.972	0.969	0.969
32	0.5	0.50	1.0	1.1	0.964	0.955	0.964	0.954	0.963	0.953
32	0.5	0.50	1.0	3.0	0.969	0.956	0.964	0.968	0.969	0.965
32	0.5	0.50	1.1	1.1	0.963	0.960	0.969	0.968	0.969	0.968
32	0.5	0.50	1.1	3.0	0.967	0.960	0.966	0.975	0.962	0.968
32	0.5	0.50	3.0	1.1	0.969	0.963	0.968	0.965	0.967	0.961
32	0.5	0.50	3.0	3.0	0.973	0.959	0.972	0.966	0.973	0.968
96	0.1	0.25	1.0	1.1	0.973	0.979	0.974	0.980	0.973	0.980
96	0.1	0.25	1.0	3.0	0.959	0.971	0.956	0.971	0.960	0.979
96	0.1	0.25	1.1	1.1	0.974	0.978	0.974	0.979	0.971	0.980
96	0.1	0.25	1.1	3.0	0.962	0.971	0.959	0.974	0.959	0.978
96	0.1	0.25	3.0	1.1	0.972	0.974	0.975	0.977	0.972	0.974
96	0.1	0.25	3.0	3.0	0.963	0.966	0.968	0.972	0.962	0.969
96	0.1	0.50	1.0	1.1	0.974	0.980	0.974	0.981	0.971	0.980
96	0.1	0.50	1.0	3.0	0.951	0.974	0.953	0.977	0.950	0.972
96	0.1	0.50	1.1	1.1	0.972	0.978	0.974	0.980	0.972	0.977
96	0.1	0.50	1.1	3.0	0.950	0.972	0.955	0.977	0.949	0.973

96	0.1	0.50	3.0	1.1	0.974	0.974	0.979	0.978	0.976	0.974
96	0.1	0.50	3.0	3.0	0.961	0.966	0.958	0.970	0.961	0.974
96	0.5	0.25	1.0	1.1	0.954	0.953	0.952	0.950	0.958	0.954
96	0.5	0.25	1.0	3.0	0.951	0.951	0.952	0.957	0.955	0.957
96	0.5	0.25	1.1	1.1	0.957	0.956	0.954	0.952	0.956	0.952
96	0.5	0.25	1.1	3.0	0.950	0.952	0.952	0.957	0.953	0.957
96	0.5	0.25	3.0	1.1	0.955	0.956	0.954	0.954	0.957	0.954
96	0.5	0.25	3.0	3.0	0.952	0.944	0.952	0.952	0.957	0.951
96	0.5	0.50	1.0	1.1	0.953	0.951	0.952	0.948	0.949	0.946
96	0.5	0.50	1.0	3.0	0.955	0.950	0.956	0.963	0.951	0.956
96	0.5	0.50	1.1	1.1	0.956	0.955	0.951	0.950	0.954	0.951
96	0.5	0.50	1.1	3.0	0.960	0.952	0.956	0.964	0.956	0.961
96	0.5	0.50	3.0	1.1	0.952	0.953	0.953	0.953	0.952	0.954
96	0.5	0.50	3.0	3.0	0.953	0.937	0.954	0.953	0.950	0.946

3.2 Batch 2: Binary Outcome, Continuous Predictors

Table 3.4: Batch 2 (Binary Y, Continuous X): Power

n	Pr(Y)	bZ	bX	Model-based				Rerandomization		
				CR		SBR		CAA		CAA
				adj	unadj	adj	unadj	adj	unadj	adj
32	0.1	1.0	1.1	0.068	0.001	0.073	0.000	0.068	0.001	0.061
32	0.1	1.0	3.0	0.126	0.004	0.126	0.002	0.125	0.005	0.061
32	0.1	1.1	1.1	0.067	0.001	0.074	0.000	0.069	0.001	0.062
32	0.1	1.1	3.0	0.124	0.004	0.123	0.003	0.128	0.006	0.060
32	0.1	3.0	1.1	0.067	0.006	0.068	0.003	0.067	0.005	0.137
32	0.1	3.0	3.0	0.177	0.021	0.178	0.012	0.179	0.031	0.146
32	0.5	1.0	1.1	0.030	0.028	0.029	0.026	0.027	0.026	0.054
32	0.5	1.0	3.0	0.050	0.029	0.046	0.013	0.046	0.025	0.054
32	0.5	1.1	1.1	0.028	0.028	0.026	0.023	0.027	0.026	0.057
32	0.5	1.1	3.0	0.051	0.029	0.050	0.014	0.050	0.029	0.055
32	0.5	3.0	1.1	0.219	0.235	0.242	0.235	0.216	0.236	0.289
32	0.5	3.0	3.0	0.181	0.116	0.192	0.097	0.174	0.115	0.210
96	0.1	1.0	1.1	0.025	0.018	0.022	0.016	0.026	0.021	0.063
96	0.1	1.0	3.0	0.065	0.032	0.057	0.024	0.062	0.040	0.061
96	0.1	1.1	1.1	0.028	0.019	0.023	0.017	0.027	0.024	0.068
96	0.1	1.1	3.0	0.065	0.035	0.063	0.026	0.064	0.043	0.064
96	0.1	3.0	1.1	0.215	0.204	0.218	0.214	0.209	0.201	0.346
96	0.1	3.0	3.0	0.390	0.272	0.400	0.268	0.392	0.284	0.398
96	0.5	1.0	1.1	0.045	0.049	0.046	0.053	0.043	0.046	0.063
96	0.5	1.0	3.0	0.049	0.047	0.050	0.035	0.046	0.052	0.065
96	0.5	1.1	1.1	0.047	0.050	0.050	0.055	0.053	0.057	0.073
96	0.5	1.1	3.0	0.056	0.053	0.055	0.037	0.051	0.059	0.069
96	0.5	3.0	1.1	0.718	0.727	0.721	0.742	0.714	0.727	0.718
96	0.5	3.0	3.0	0.568	0.447	0.560	0.442	0.562	0.444	0.563

Table 3.5: Batch 2 (Binary Y, Continuous X): Median bias

n	Pr(Y)	bZ	bX	Model-based				Rerandomization		
				CR		SBR		CAA		CAA
				adj	unadj	adj	unadj	adj	unadj	adj
32	0.1	1.0	1.1	0.000	0.000	0.000	0.000	0.000	0.000	0.000
32	0.1	1.0	3.0	0.014	0.000	-0.019	0.000	0.047	0.000	0.047
32	0.1	1.1	1.1	-0.048	-0.065	-0.065	-0.095	0.005	-0.044	0.005
32	0.1	1.1	3.0	0.031	-0.049	0.007	-0.095	0.044	0.022	0.044
32	0.1	3.0	1.1	0.354	0.143	0.311	0.143	0.366	0.143	0.366
32	0.1	3.0	3.0	0.332	-0.198	0.332	-0.236	0.354	-0.198	0.354
32	0.5	1.0	1.1	0.012	0.000	-0.014	0.000	-0.012	0.000	-0.012
32	0.5	1.0	3.0	0.017	0.000	-0.002	0.000	0.016	0.000	0.016
32	0.5	1.1	1.1	0.011	-0.026	0.010	-0.031	0.001	-0.031	0.001
32	0.5	1.1	3.0	0.047	-0.031	0.040	-0.080	0.021	-0.029	0.021
32	0.5	3.0	1.1	0.144	0.036	0.175	0.041	0.152	0.031	0.152
32	0.5	3.0	3.0	0.158	-0.310	0.194	-0.325	0.165	-0.310	0.165
96	0.1	1.0	1.1	0.014	0.000	0.003	0.000	0.002	0.000	0.002
96	0.1	1.0	3.0	0.013	0.000	-0.004	0.000	0.013	0.000	0.013
96	0.1	1.1	1.1	0.010	0.004	0.002	-0.002	0.015	0.009	0.015
96	0.1	1.1	3.0	0.015	-0.026	-0.001	-0.044	0.027	-0.012	0.027
96	0.1	3.0	1.1	0.076	0.039	0.090	0.047	0.075	0.039	0.075
96	0.1	3.0	3.0	0.075	-0.251	0.078	-0.260	0.078	-0.234	0.078
96	0.5	1.0	1.1	0.009	0.000	-0.014	-0.002	0.001	0.000	0.001
96	0.5	1.0	3.0	-0.001	0.000	-0.006	0.000	0.000	0.000	0.000
96	0.5	1.1	1.1	0.013	-0.001	-0.014	-0.012	0.013	0.000	0.013
96	0.5	1.1	3.0	0.008	-0.015	0.000	-0.018	0.005	-0.015	0.005
96	0.5	3.0	1.1	0.037	0.011	0.026	0.013	0.033	0.011	0.033
96	0.5	3.0	3.0	0.057	-0.323	0.034	-0.336	0.061	-0.323	0.061

Table 3.6: Batch 2 (Binary Y, Continuous X): Coverage probability

n	Pr(Y)	bZ	bX	Model-based					
				CR		SBR		CAA	
				adj	unadj	adj	unadj	adj	unadj
32	0.1	1.0	1.1	0.930	0.999	0.924	1.000	0.929	0.999
32	0.1	1.0	3.0	0.862	0.993	0.860	0.997	0.863	0.991
32	0.1	1.1	1.1	0.932	0.999	0.925	1.000	0.930	0.999
32	0.1	1.1	3.0	0.867	0.994	0.865	0.996	0.861	0.991
32	0.1	3.0	1.1	0.913	0.970	0.909	0.970	0.910	0.966
32	0.1	3.0	3.0	0.868	0.967	0.872	0.978	0.870	0.964
32	0.5	1.0	1.1	0.960	0.956	0.958	0.948	0.965	0.960
32	0.5	1.0	3.0	0.940	0.955	0.941	0.971	0.943	0.960
32	0.5	1.1	1.1	0.963	0.962	0.965	0.968	0.963	0.962
32	0.5	1.1	3.0	0.938	0.960	0.939	0.978	0.941	0.962
32	0.5	3.0	1.1	0.966	0.964	0.966	0.963	0.966	0.964
32	0.5	3.0	3.0	0.935	0.940	0.941	0.961	0.934	0.940
96	0.1	1.0	1.1	0.973	0.980	0.976	0.981	0.971	0.977
96	0.1	1.0	3.0	0.931	0.968	0.939	0.975	0.933	0.958
96	0.1	1.1	1.1	0.972	0.980	0.976	0.982	0.970	0.976
96	0.1	1.1	3.0	0.934	0.967	0.937	0.973	0.933	0.954
96	0.1	3.0	1.1	0.978	0.978	0.980	0.978	0.976	0.978
96	0.1	3.0	3.0	0.935	0.927	0.934	0.933	0.932	0.917
96	0.5	1.0	1.1	0.951	0.947	0.949	0.945	0.954	0.951
96	0.5	1.0	3.0	0.947	0.951	0.945	0.963	0.951	0.945
96	0.5	1.1	1.1	0.954	0.951	0.954	0.951	0.949	0.947
96	0.5	1.1	3.0	0.943	0.951	0.943	0.963	0.953	0.940
96	0.5	3.0	1.1	0.951	0.952	0.954	0.954	0.951	0.951
96	0.5	3.0	3.0	0.947	0.879	0.946	0.891	0.944	0.874

Table 3.7: Batch 2 (Binary Y, Continuous X): Power, subsetted

Avg. nsims	n	Pr(Y)	bZ	bX	Model-based				Rerandomization		
					CR		SBR		CAA		
					adj	unadj	adj	unadj	adj	unadj	
3469 (69.2%)	32	0.1	1.0	1.1	0.011	0.001	0.011	0.000	0.012	0.001	0.014
4320 (86.2%)	32	0.1	1.0	3.0	0.058	0.004	0.060	0.002	0.059	0.006	0.027
3462 (69.1%)	32	0.1	1.1	1.1	0.011	0.001	0.012	0.000	0.013	0.001	0.014
4318 (86.2%)	32	0.1	1.1	3.0	0.057	0.005	0.060	0.003	0.063	0.006	0.027
3048 (60.8%)	32	0.1	3.0	1.1	0.025	0.009	0.019	0.005	0.028	0.008	0.037
4123 (82.3%)	32	0.1	3.0	3.0	0.127	0.025	0.131	0.014	0.134	0.038	0.088
5008 (100%)	32	0.5	1.0	1.1	0.030	0.028	0.029	0.026	0.027	0.026	0.054
4999 (99.8%)	32	0.5	1.0	3.0	0.047	0.029	0.043	0.013	0.044	0.025	0.054
5010 (100%)	32	0.5	1.1	1.1	0.028	0.028	0.026	0.023	0.027	0.026	0.057
4996 (99.7%)	32	0.5	1.1	3.0	0.048	0.029	0.048	0.014	0.047	0.028	0.054
4999 (99.8%)	32	0.5	3.0	1.1	0.219	0.235	0.242	0.235	0.216	0.236	0.288
4982 (99.4%)	32	0.5	3.0	3.0	0.175	0.116	0.190	0.097	0.169	0.114	0.206
4934 (98.5%)	96	0.1	1.0	1.1	0.025	0.018	0.022	0.017	0.027	0.021	0.054
5009 (100%)	96	0.1	1.0	3.0	0.065	0.032	0.057	0.024	0.062	0.040	0.061
4929 (98.4%)	96	0.1	1.1	1.1	0.028	0.019	0.023	0.018	0.027	0.024	0.058
5009 (100%)	96	0.1	1.1	3.0	0.066	0.035	0.063	0.026	0.064	0.043	0.064
4745 (94.7%)	96	0.1	3.0	1.1	0.227	0.215	0.229	0.225	0.221	0.213	0.313
5001 (99.8%)	96	0.1	3.0	3.0	0.391	0.272	0.400	0.269	0.392	0.284	0.397
5010 (100%)	96	0.5	1.0	1.1	0.045	0.049	0.046	0.053	0.043	0.046	0.063
5010 (100%)	96	0.5	1.0	3.0	0.049	0.047	0.050	0.035	0.046	0.052	0.065
5010 (100%)	96	0.5	1.1	1.1	0.047	0.050	0.050	0.055	0.053	0.057	0.073
5010 (100%)	96	0.5	1.1	3.0	0.056	0.053	0.055	0.037	0.051	0.059	0.069
5010 (100%)	96	0.5	3.0	1.1	0.718	0.727	0.721	0.742	0.714	0.727	0.718
5010 (100%)	96	0.5	3.0	3.0	0.568	0.447	0.560	0.442	0.562	0.444	0.563

3.3 Batch 3: Continuous Outcome, Binary Predictors

Table 3.8: Batch 3 (Continuous Y, Binary X): Power

Table 3.9: Batch 3 (Continuous Y, Binary X): Median bias

n	Pr(X)	bZ	bX	Model-based				Rerandomization		
				CR		SBR		CAA		CAA
				adj	unadj	adj	unadj	adj	unadj	adj
32	0.25	1	1.1	0.005	0.005	0.009	0.008	0.003	-0.003	0.003
32	0.25	1	3.0	0.005	-0.003	0.009	-0.003	0.003	-0.089	0.003
32	0.25	3	1.1	0.005	0.005	0.009	0.008	0.003	-0.003	0.003
32	0.25	3	3.0	0.005	-0.003	0.009	-0.003	0.003	-0.089	0.003
32	0.50	1	1.1	0.005	0.006	0.003	-0.003	0.004	0.005	0.004
32	0.50	1	3.0	0.005	-0.006	0.003	0.001	0.004	0.045	0.004
32	0.50	3	1.1	0.005	0.006	0.003	-0.003	0.004	0.005	0.004
32	0.50	3	3.0	0.005	-0.006	0.003	0.001	0.004	0.045	0.004
96	0.25	1	1.1	-0.002	-0.006	0.001	0.000	-0.002	-0.010	-0.002
96	0.25	1	3.0	-0.002	-0.007	0.001	0.001	-0.002	-0.142	-0.002
96	0.25	3	1.1	-0.002	-0.006	0.001	0.000	-0.002	-0.010	-0.002
96	0.25	3	3.0	-0.002	-0.007	0.001	0.001	-0.002	-0.142	-0.002
96	0.50	1	1.1	-0.004	-0.004	0.001	0.002	-0.002	-0.004	-0.002
96	0.50	1	3.0	-0.004	0.001	0.001	0.003	-0.002	0.018	-0.002
96	0.50	3	1.1	-0.004	-0.004	0.001	0.001	0.002	-0.002	-0.004
96	0.50	3	3.0	-0.004	0.001	0.001	0.003	-0.002	0.018	-0.002

Table 3.10: Batch 3 (Continuous Y, Binary X): Coverage probability

n	Pr(X)	bZ	bX	Model-based					
				CR		SBR		CAA	
				adj	unadj	adj	unadj	adj	unadj
32	0.25	1	1.1	0.937	0.937	0.933	0.934	0.938	0.940
32	0.25	1	3.0	0.937	0.945	0.933	0.982	0.938	0.931
32	0.25	3	1.1	0.937	0.937	0.933	0.934	0.938	0.940
32	0.25	3	3.0	0.937	0.945	0.933	0.982	0.938	0.931
32	0.50	1	1.1	0.935	0.935	0.941	0.941	0.934	0.935
32	0.50	1	3.0	0.935	0.941	0.941	0.996	0.934	0.928
32	0.50	3	1.1	0.935	0.935	0.941	0.941	0.934	0.935
32	0.50	3	3.0	0.935	0.941	0.941	0.996	0.934	0.928
96	0.25	1	1.1	0.948	0.950	0.950	0.948	0.951	0.947
96	0.25	1	3.0	0.948	0.943	0.950	0.987	0.951	0.924
96	0.25	3	1.1	0.948	0.950	0.950	0.948	0.951	0.947
96	0.25	3	3.0	0.948	0.943	0.950	0.987	0.951	0.924
96	0.50	1	1.1	0.948	0.947	0.955	0.957	0.951	0.951
96	0.50	1	3.0	0.948	0.942	0.955	0.997	0.951	0.901
96	0.50	3	1.1	0.948	0.947	0.955	0.957	0.951	0.951
96	0.50	3	3.0	0.948	0.942	0.955	0.997	0.951	0.901

3.4 Batch 4: Continuous Outcome, Continuous Predictors

Table 3.11: Batch 4 (Continuous Y, Continuous X): Power

n	bZ	bX	Model-based				Rerandomization			
			CR		SBR		CAA		CAA	
			adj	unadj	adj	unadj	adj	unadj	adj	adj
32	1.0	1.1	0.051	0.048	0.052	0.054	0.051	0.048	0.054	
32	1.0	3.0	0.051	0.049	0.052	0.007	0.051	0.049	0.054	
32	1.1	1.1	0.060	0.059	0.061	0.062	0.060	0.059	0.058	
32	1.1	3.0	0.060	0.051	0.061	0.008	0.060	0.051	0.058	
32	3.0	1.1	0.999	0.999	0.999	0.999	0.999	0.999	0.999	
32	3.0	3.0	0.999	0.435	0.999	0.419	0.999	0.435	0.999	
96	1.0	1.1	0.052	0.051	0.049	0.049	0.052	0.051	0.054	
96	1.0	3.0	0.052	0.049	0.049	0.005	0.052	0.049	0.054	
96	1.1	1.1	0.079	0.079	0.074	0.074	0.079	0.079	0.084	
96	1.1	3.0	0.079	0.052	0.074	0.006	0.079	0.052	0.084	
96	3.0	1.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	
96	3.0	3.0	1.000	0.895	1.000	0.961	1.000	0.895	1.000	

Table 3.12: Batch 4 (Continuous Y, Continuous X): Median bias

n	bZ	bX	Model-based				Rerandomization		
			CR		SBR		CAA		
			adj	unadj	adj	unadj	adj	unadj	
32	1.0	1.1	-0.013	-0.009	0.002	-0.006	-0.013	-0.009	-0.013
32	1.0	3.0	-0.013	-0.019	0.002	-0.002	-0.013	-0.019	-0.013
32	1.1	1.1	-0.013	-0.009	0.002	-0.006	-0.013	-0.009	-0.013
32	1.1	3.0	-0.013	-0.019	0.002	-0.002	-0.013	-0.019	-0.013
32	3.0	1.1	-0.013	-0.009	0.002	-0.006	-0.013	-0.009	-0.013
32	3.0	3.0	-0.013	-0.019	0.002	-0.002	-0.013	-0.019	-0.013
96	1.0	1.1	-0.003	-0.004	0.002	0.003	-0.003	-0.004	-0.003
96	1.0	3.0	-0.003	-0.013	0.002	-0.002	-0.003	-0.013	-0.003
96	1.1	1.1	-0.003	-0.004	0.002	0.003	-0.003	-0.004	-0.003
96	1.1	3.0	-0.003	-0.013	0.002	-0.002	-0.003	-0.013	-0.003
96	3.0	1.1	-0.003	-0.004	0.002	0.003	-0.003	-0.004	-0.003
96	3.0	3.0	-0.003	-0.013	0.002	-0.002	-0.003	-0.013	-0.003

Table 3.13: Batch 4 (Continuous Y, Continuous X): Coverage probability

Model-based									
n	bZ	bX	CR		SBR		CAA		
			adj	unadj	adj	unadj	adj	unadj	
32	1.0	1.1	0.938	0.941	0.939	0.937	0.938	0.941	
32	1.0	3.0	0.938	0.940	0.939	0.991	0.938	0.940	
32	1.1	1.1	0.938	0.941	0.939	0.937	0.938	0.941	
32	1.1	3.0	0.938	0.940	0.939	0.991	0.938	0.940	
32	3.0	1.1	0.938	0.941	0.939	0.937	0.938	0.941	
32	3.0	3.0	0.938	0.940	0.939	0.991	0.938	0.940	
96	1.0	1.1	0.946	0.947	0.949	0.948	0.946	0.947	
96	1.0	3.0	0.946	0.949	0.949	0.994	0.946	0.949	
96	1.1	1.1	0.946	0.947	0.949	0.948	0.946	0.947	
96	1.1	3.0	0.946	0.949	0.949	0.994	0.946	0.949	
96	3.0	1.1	0.946	0.947	0.949	0.948	0.946	0.947	
96	3.0	3.0	0.946	0.949	0.949	0.994	0.946	0.949	

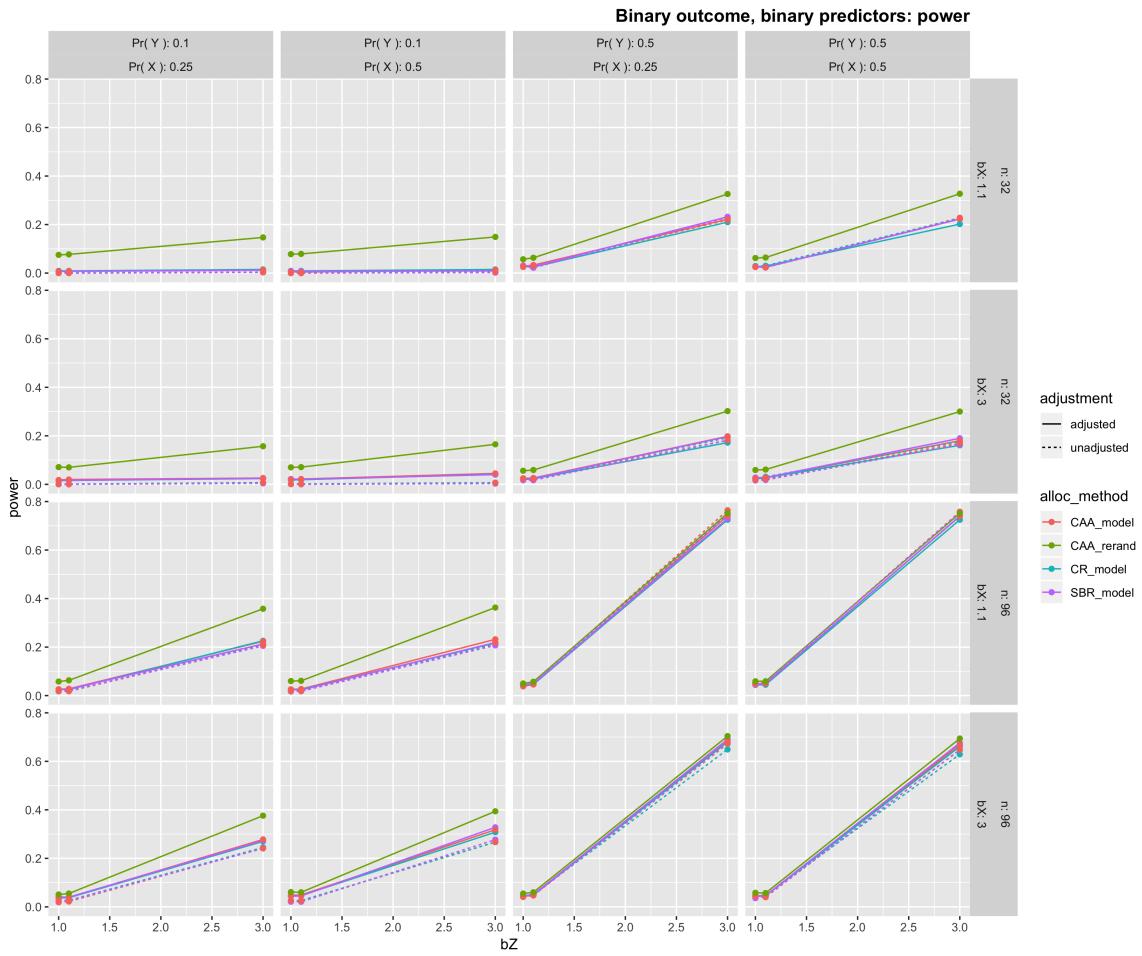


Figure 3.1: Batch 1: Power

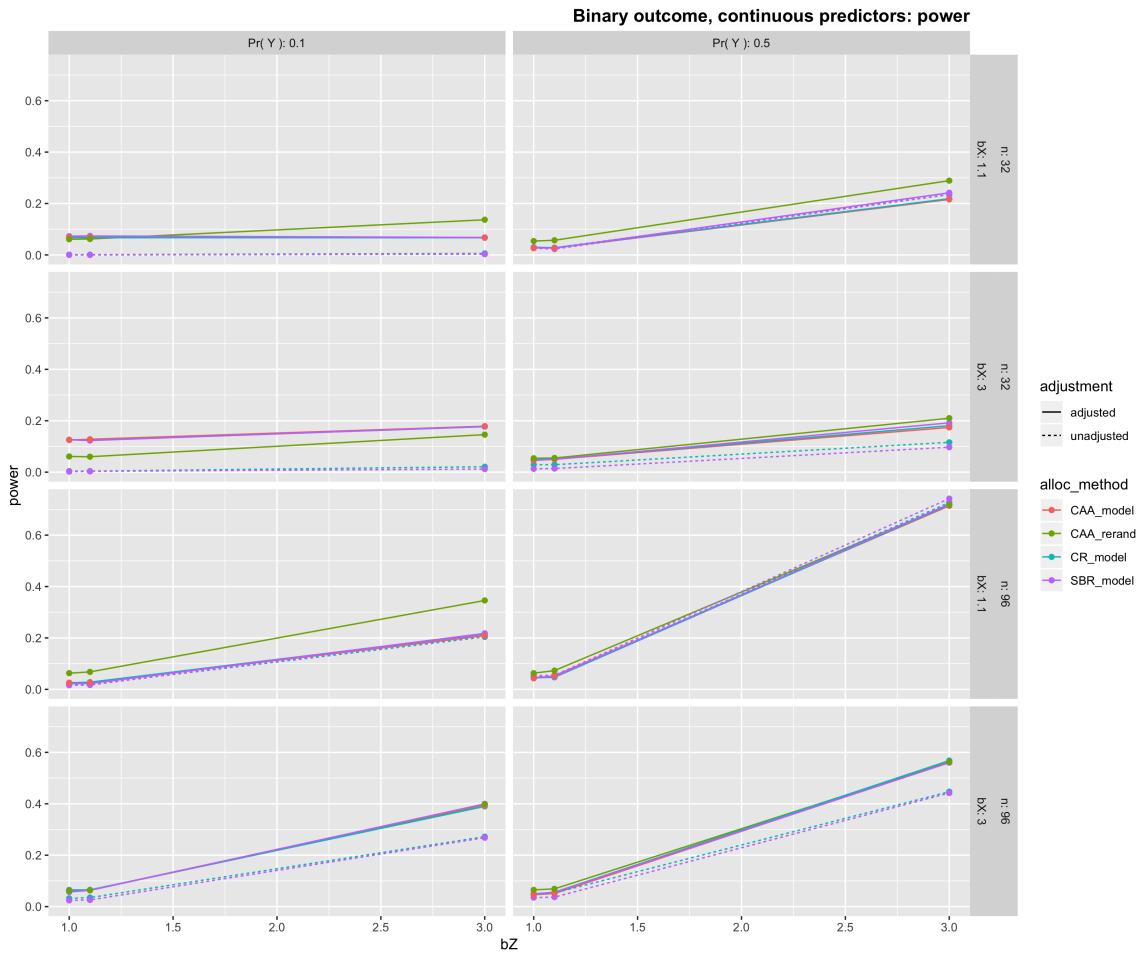


Figure 3.2: Batch 2: Power

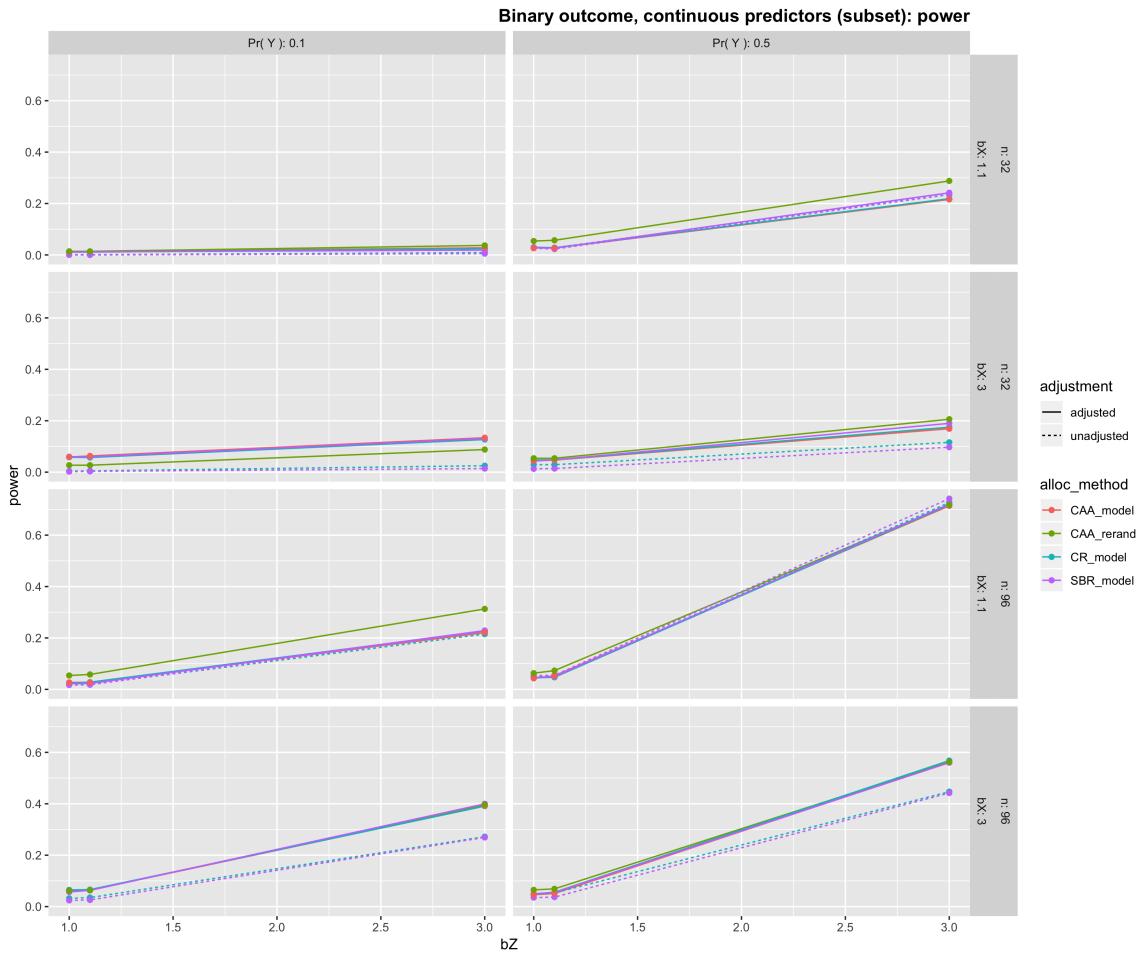


Figure 3.3: Batch 2 subset: Power

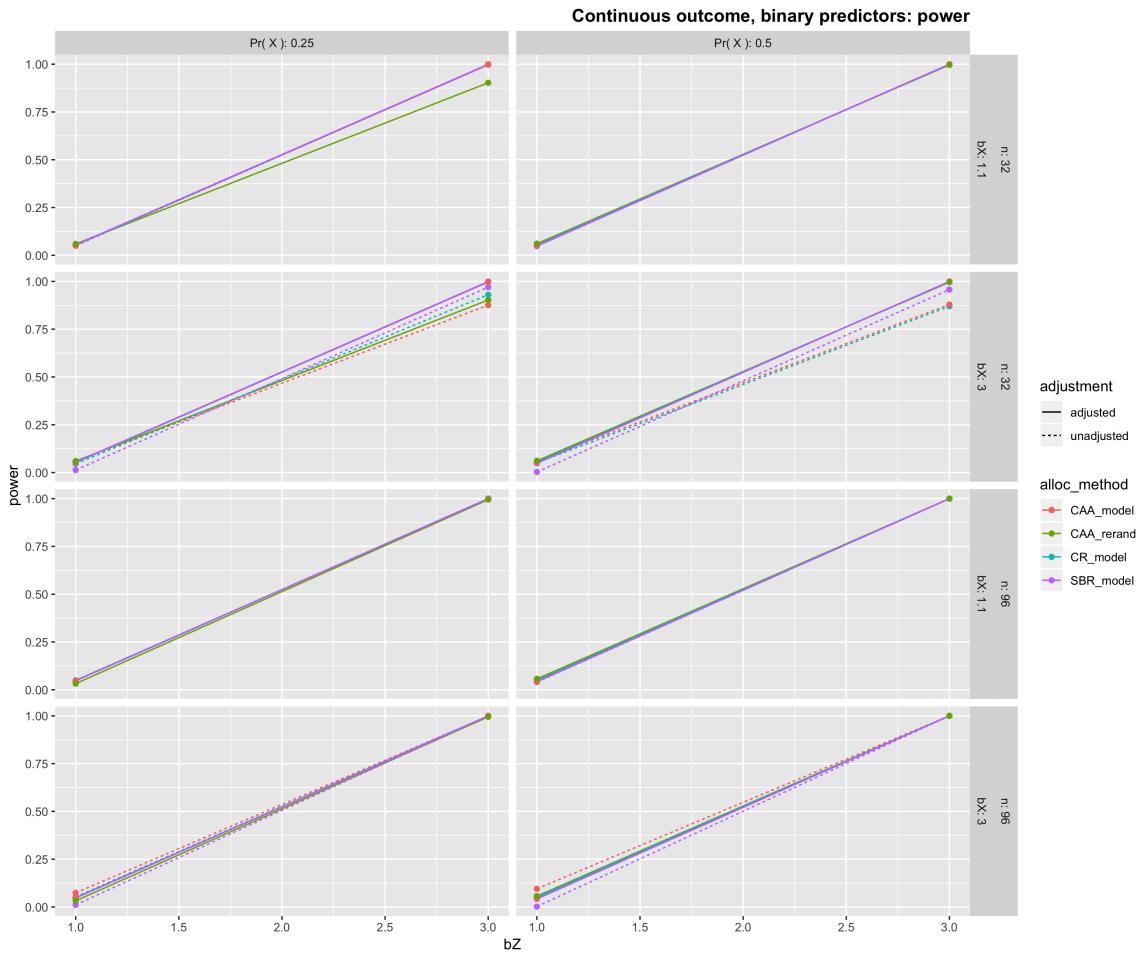


Figure 3.4: Batch 3: Power

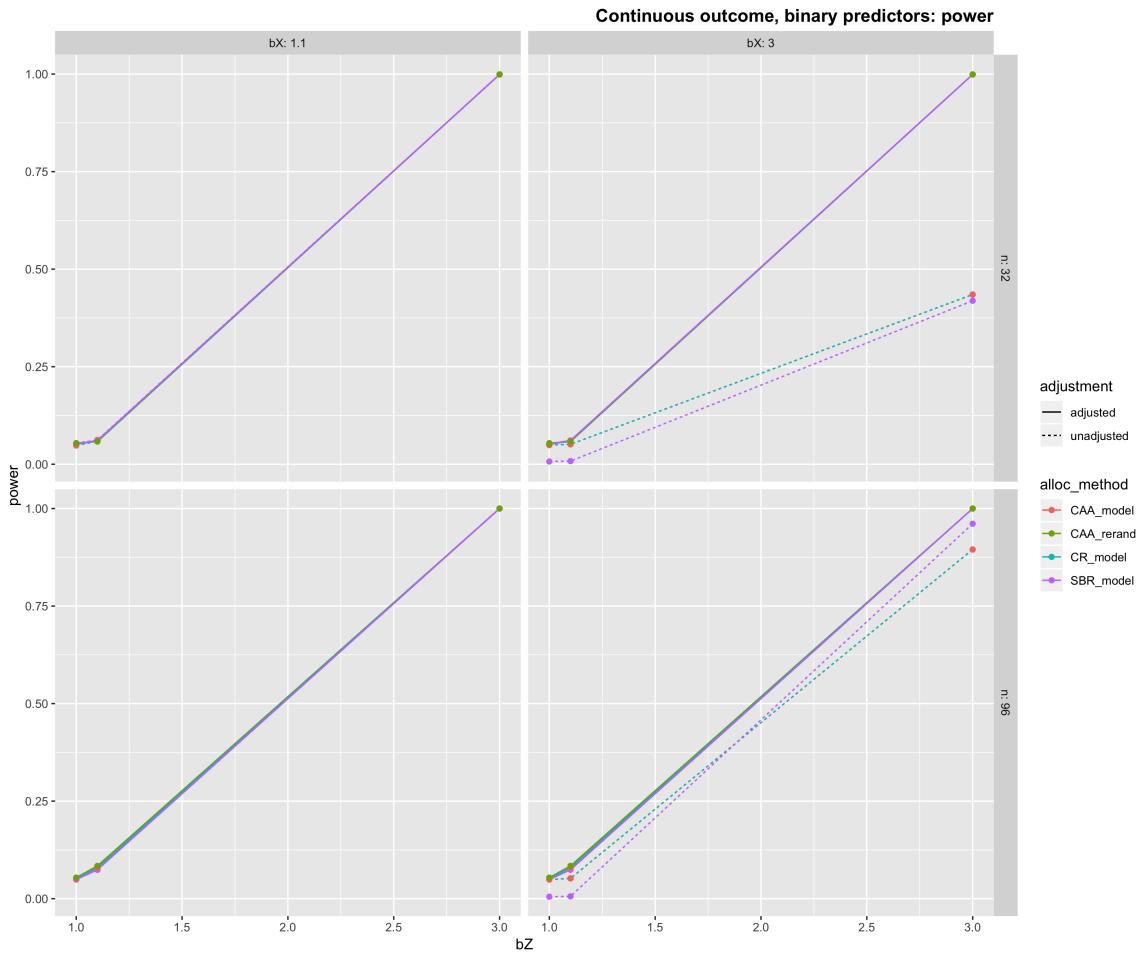


Figure 3.5: Batch 4: Power

4 Results

4.1 Binary outcome setting

Binary predictors

Power is substantially higher using CAA followed by re-randomization when compared to all other methods, including CAA followed by model-based inference. The modest increase in power is seen in low sample size settings and low marginal outcome prevalence. The trends in power for detecting the unadjusted estimate do not appear to be affected by either prognostic factor prevalence ($\text{Pr}(X)$) or effect size (bX).

The power benefit from using CAA followed by re-randomization becomes diminished when sample size increases and marginal outcome prevalence increases (see 1.1, bottom right quadrant). Even at large sample sizes re-randomization has greater power than model-based approaches, particularly when outcome prevalence is low.

Adjusting for prognostic factors used in the balancing method consistently increased power in almost all considered settings.

Median bias (Table 1.2) is adequately controlled if the estimated treatment effect is null or when trial size is large ($n=96$).

Coverage probability nears 100 percent at low outcome prevalence and low trial size. Coverage probability nears 95 percent when outcome prevalence is high and when sample size is large ($n=96$).

Subsetted simulations

Simulations with low observed event rates could result in large estimated treatment effects, often corresponding to cases where the `glm()` algorithm did not converge. For this reason, subsetted results are presented for simulation outcomes where both the `glm()` algorithm converged and at least one outcome was observed in each treatment arm.

This issue occurs more often when sample size is small ($n=32$), outcome prevalence ($Pr(Y)$) is small, and for small treatment and prognostic factor effect sizes (bZ and bX , respectively).

Subsetted simulation results Comparing these results to those subsetting on `glm()` convergence and at least one outcome occurring in each treatment group, median bias is larger in small sample size settings (see Table ??).

Subsetting on these two criterion led to excluding greater than 30 percent of simulations in low sample size scenarios.

Subsetted power results show better type I error control for CAA followed by re-randomization overall. The modest power increase remains in large sample size ($n=96$) and low outcome prevalence settings, as well as small sample size ($n=32$) and high outcome prevalence settings ($Pr(Y) = 0.5$).

Continuous predictors

In low outcome prevalence ($Pr(Y)=0.1$) under strong prognostic factor effect size ($bX = 3$), both CAA with model-based inference and SBR have higher power but fail to control size: the power under the null setting (type I error threshold of 0.05) is greater than 0.10. Looking at Table ??, power is highest with re-randomization or at least comparable to model-based approaches adjusting for prognostic factors.

Note In row 6 of Table ??, power is not higher for re-randomization. In these settings (of small sample size and low outcome prevalence), the low number of outcomes may limit the richness of the re-randomization distribution to properly model the sampling distribution of the test statistic.

Adjusting for prognostic factors used in the balancing method controls median bias, whereas the differences between unadjusted and adjusted estimates increases

with treatment assignment effect size, and becomes greater as prognostic factor effect size increases.

Coverage probability is not affected by treatment assignment effect size after adjusting for prognostic factors. Considering unadjusted estimates, treatment effect coverage probability changes with prognostic factor effect size and is markedly greater when the effect size is large ($bX = 3$).

4.2 Continuous outcome setting

Binary predictors

All methods perform comparably with respect to power. There is not as much of an advantage for re-randomization in the continuous outcome setting.

Note: *in rows 3 and 4* the power for CAA followed by rerandomization is considerably smaller than most estimates. Verify this!

Continuous predictors

Adjusting for prognostic factors considerably increases power, especially when prognostic factor effect size is large. Again, re-randomization following allocation does not confer an advantage in terms of increased power.

5 *Figures*

5.1 Batch 1: Binary Outcome, Binary Predictors

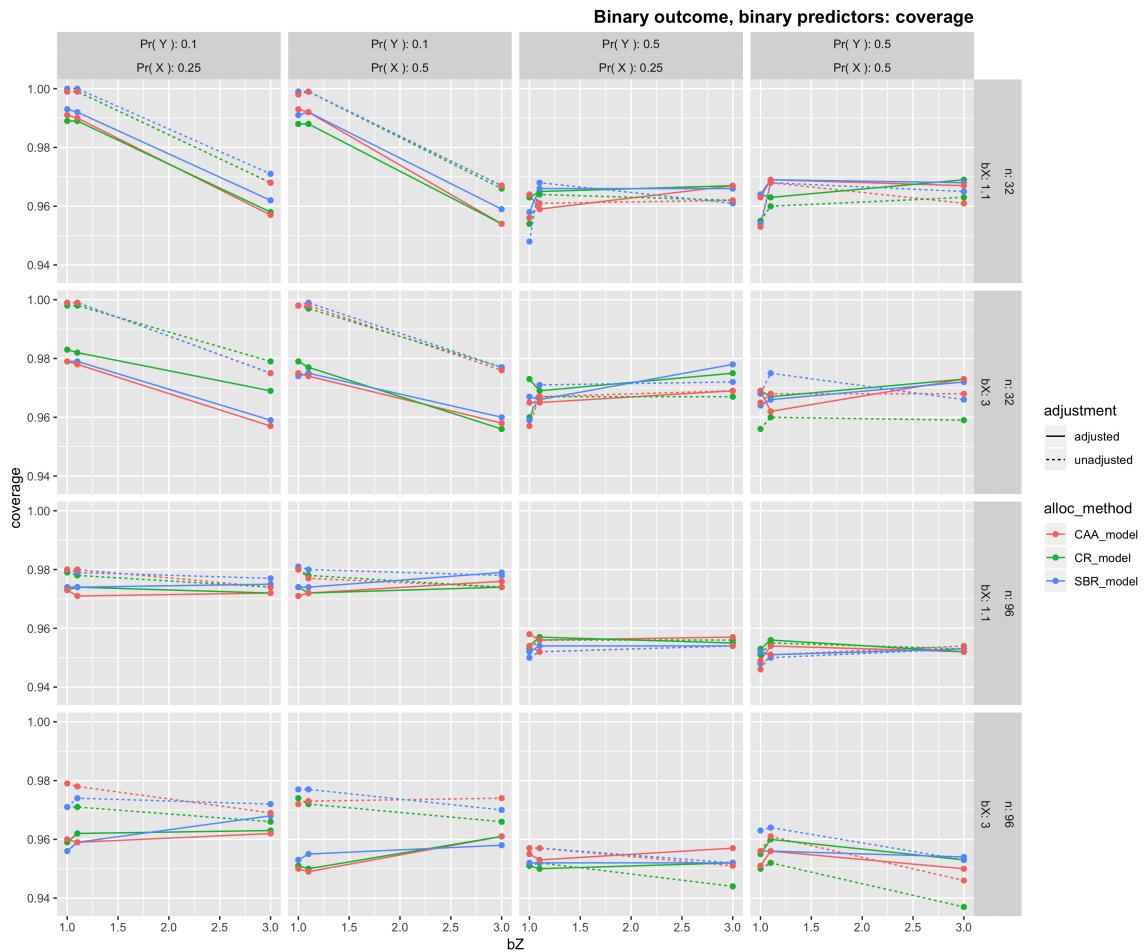


Figure 5.1: Batch 1: Coverage probability

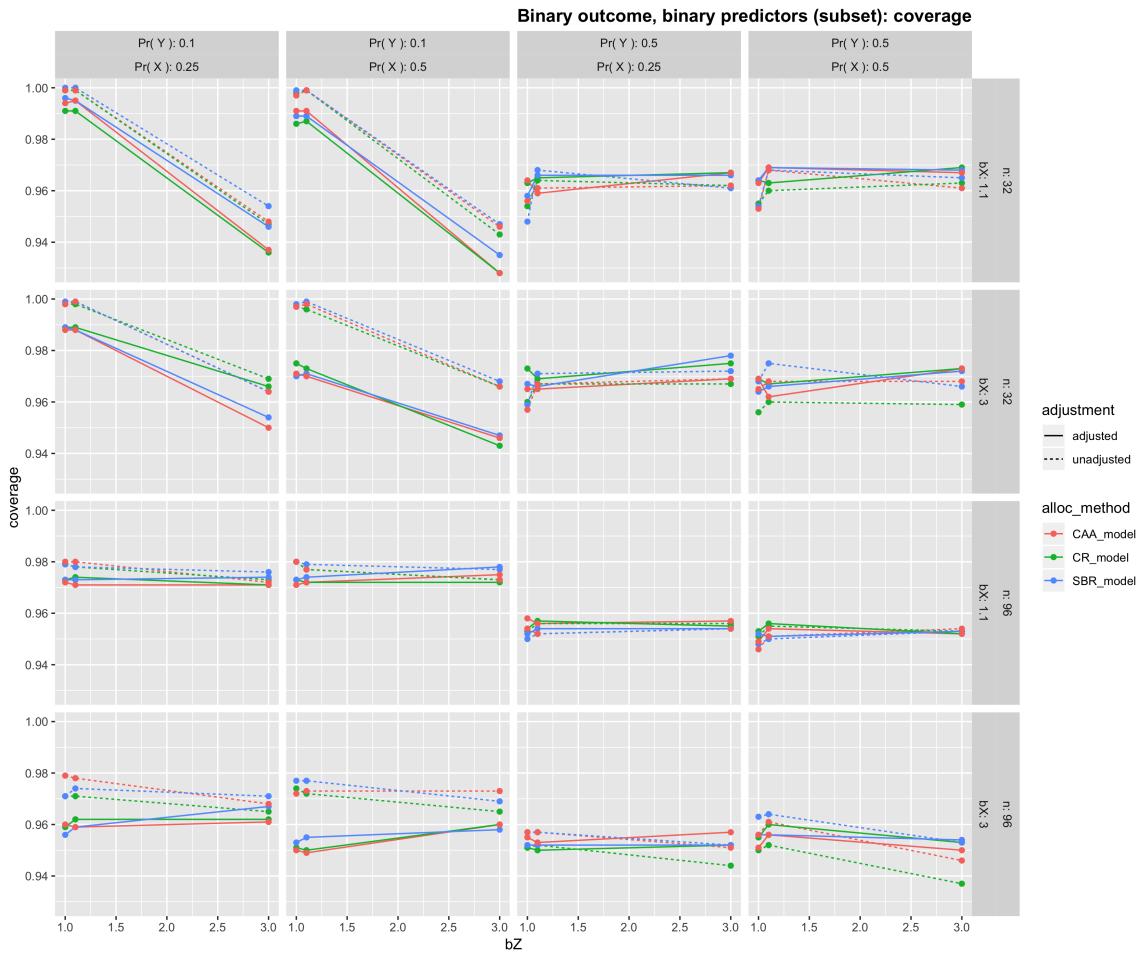


Figure 5.2: Batch 1 subset: Coverage probability

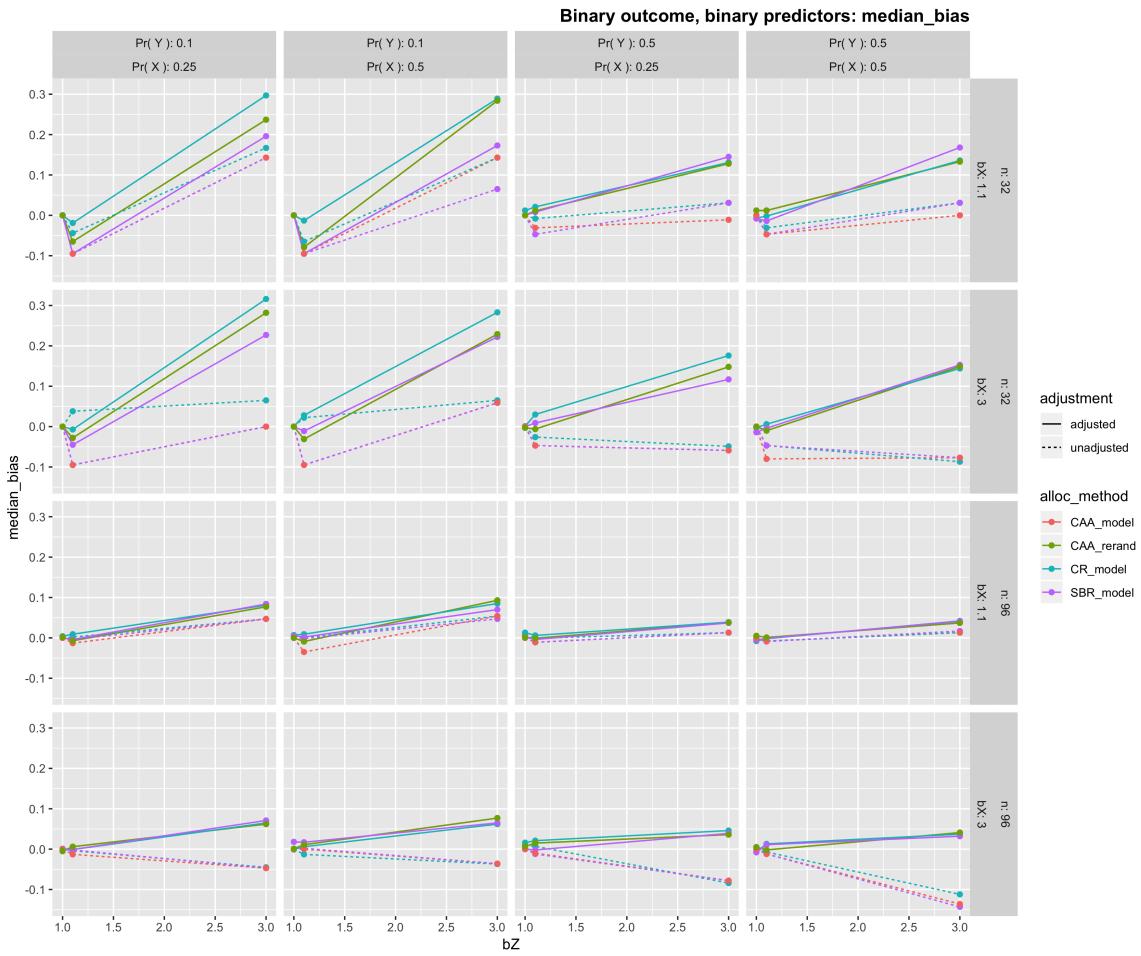


Figure 5.3: Batch 1: Median bias

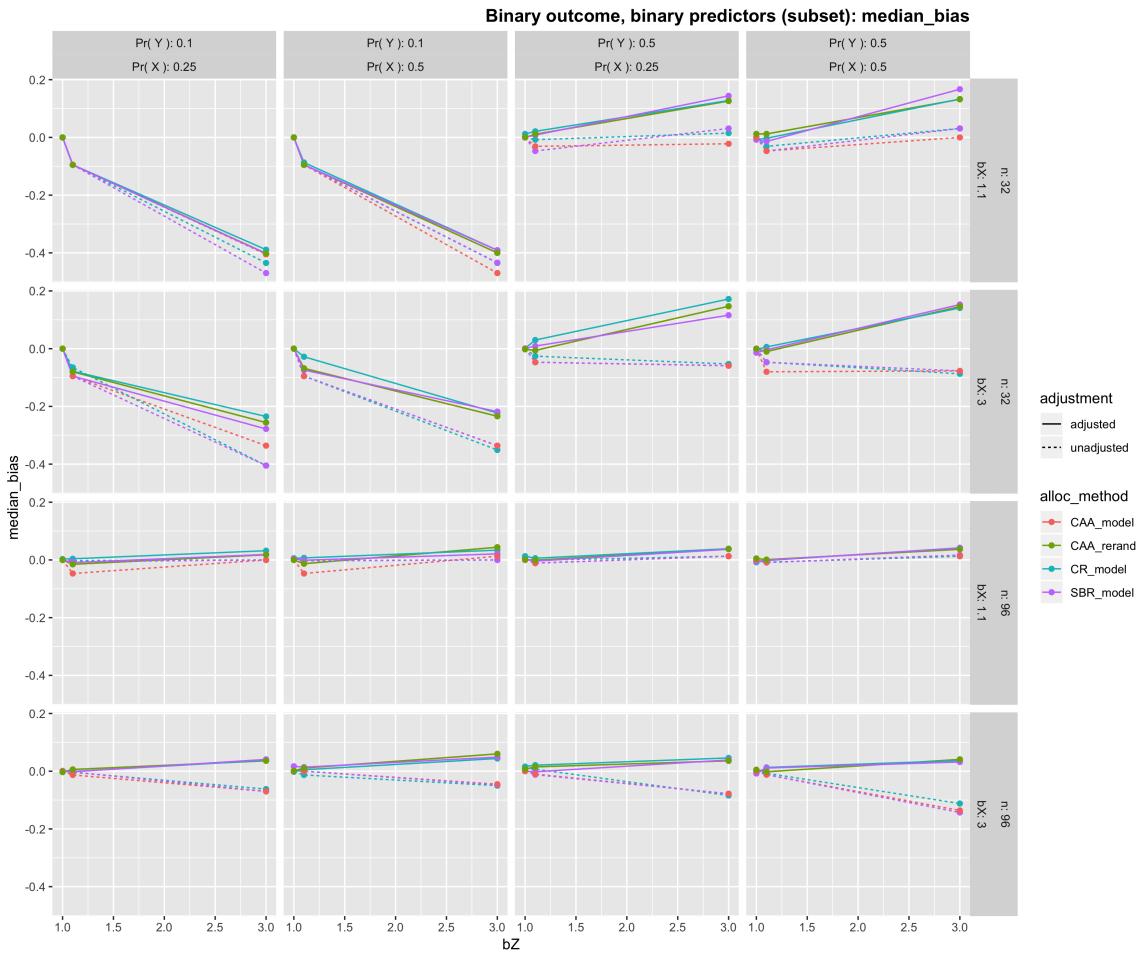


Figure 5.4: Batch 1 subset: Median bias

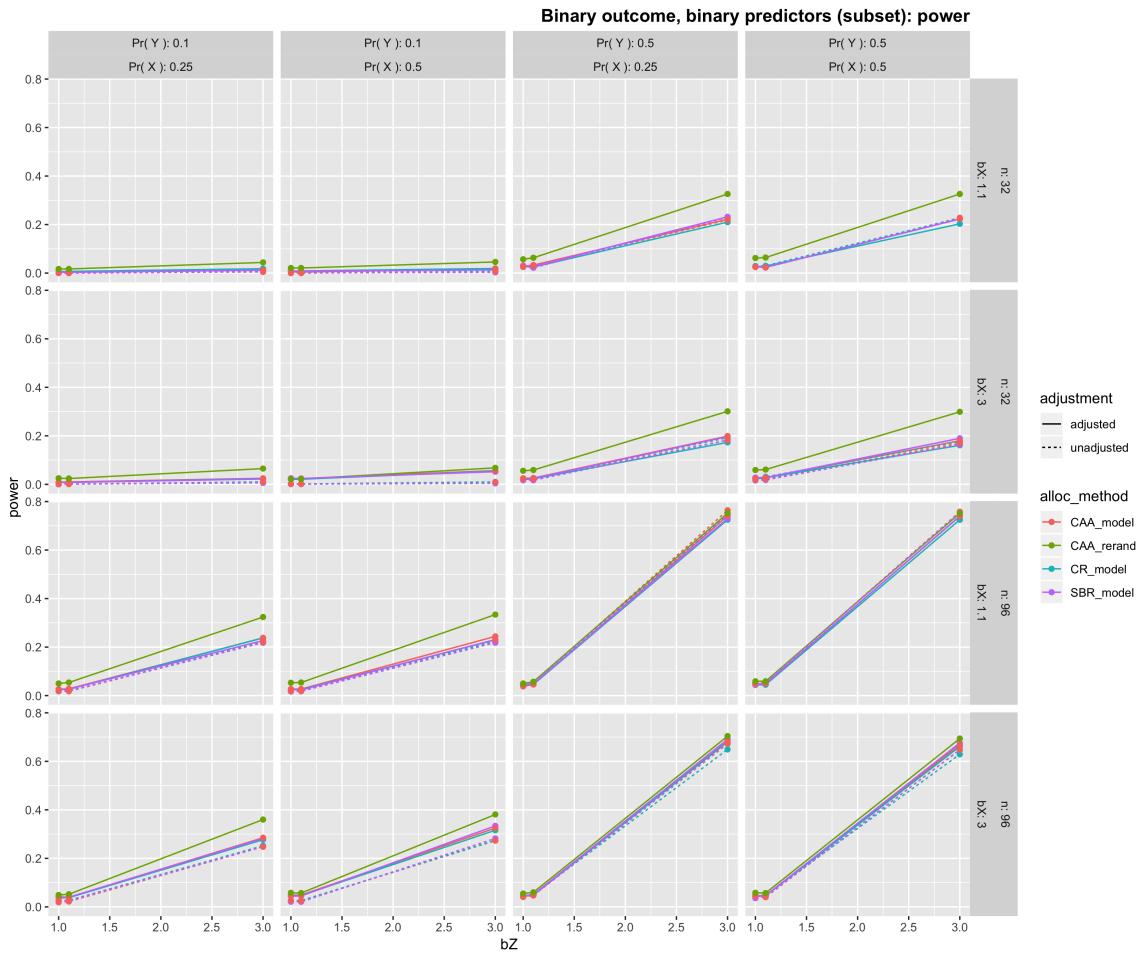


Figure 5.5: Batch 1 subset: Power

5.2 Batch 2: Binary Outcome, Continuous Predictors

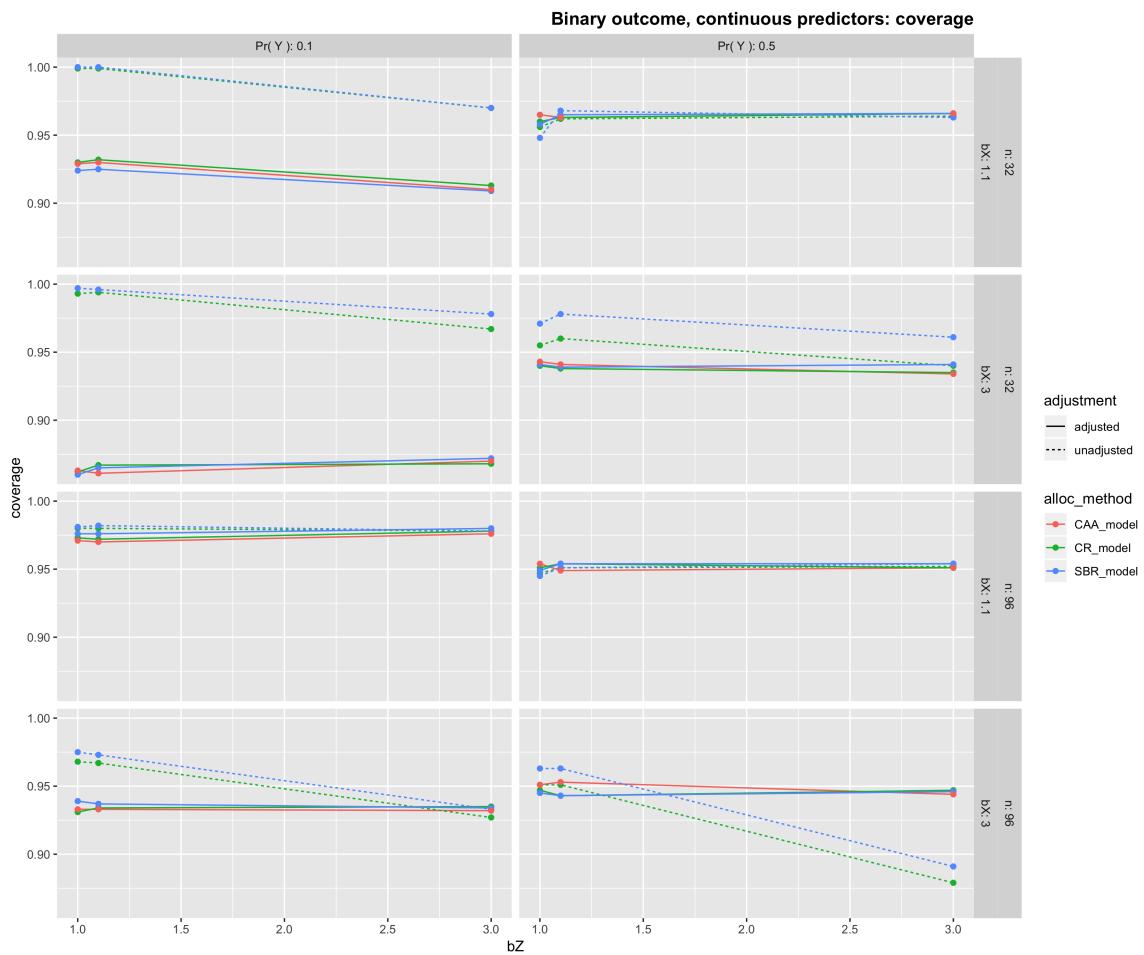


Figure 5.6: Batch 2: Coverage probability

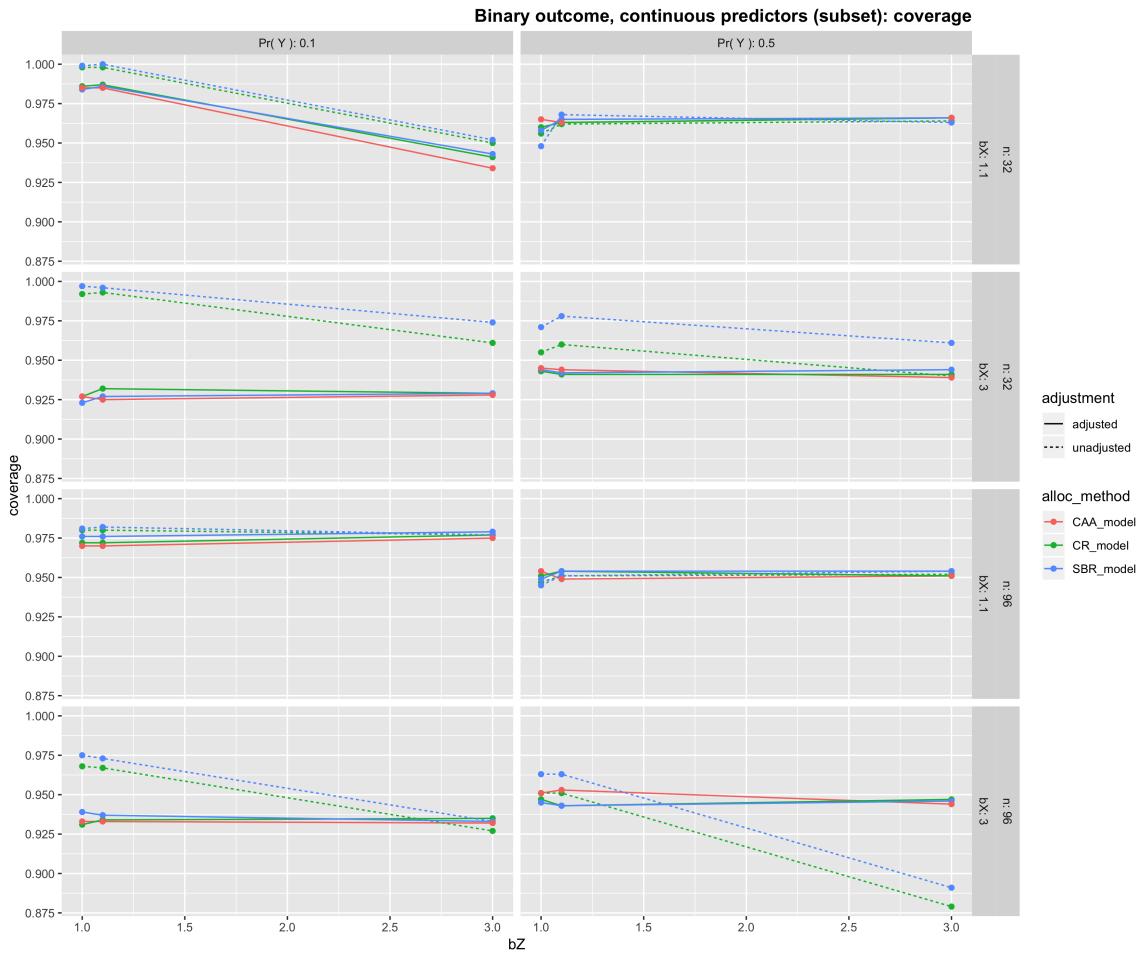


Figure 5.7: Batch 2 subset: Coverage probability

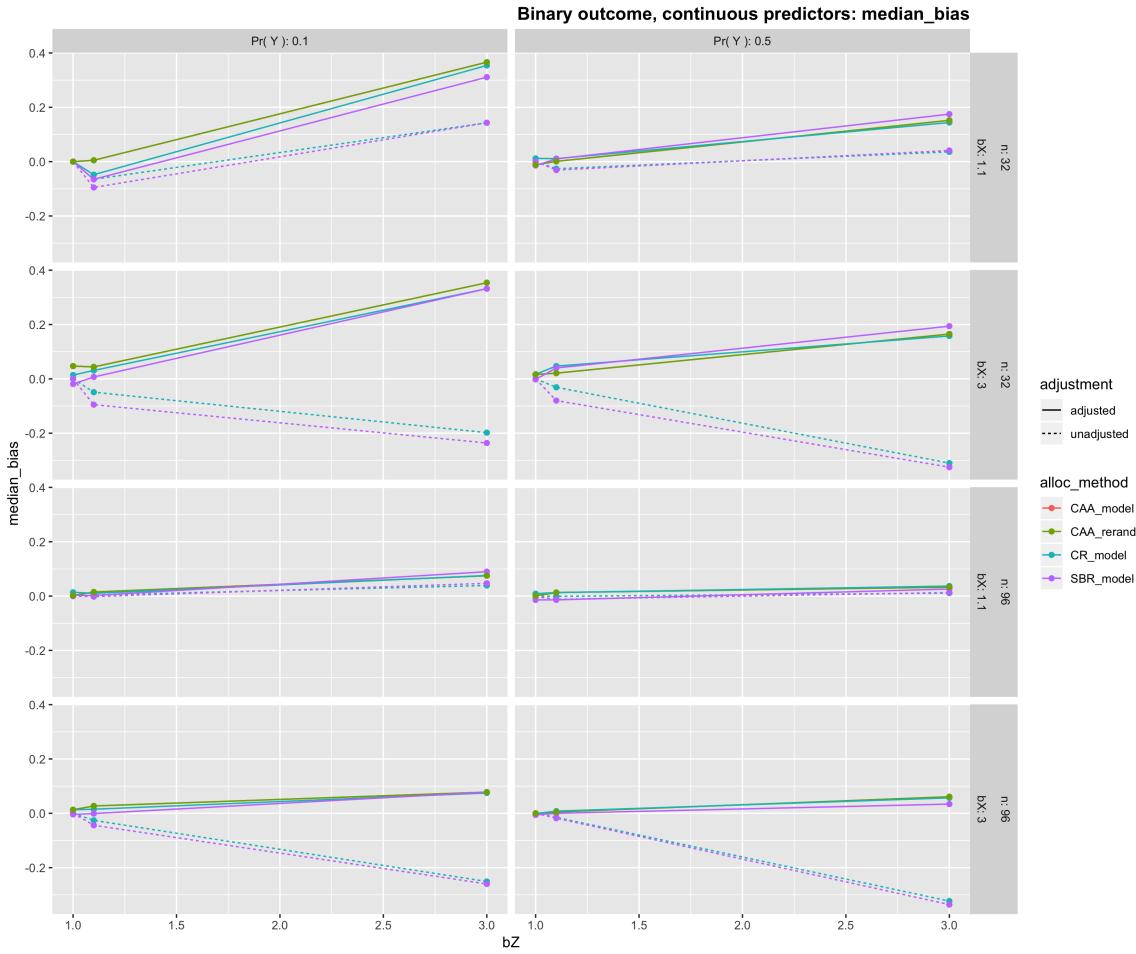


Figure 5.8: Batch 2: Median bias

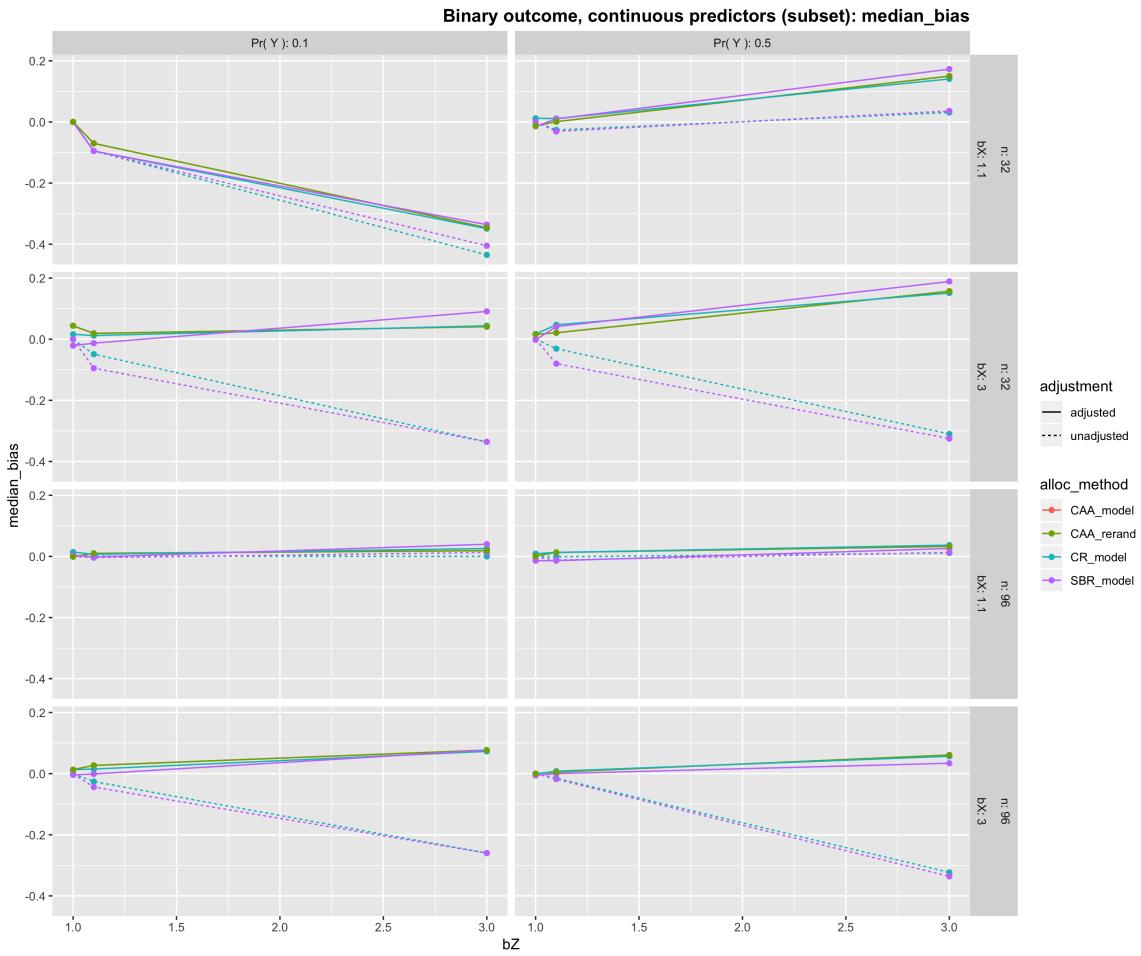


Figure 5.9: Batch 2 subset: Median bias

5.3 Batch 3: Continuous Outcome, Binary Predictors

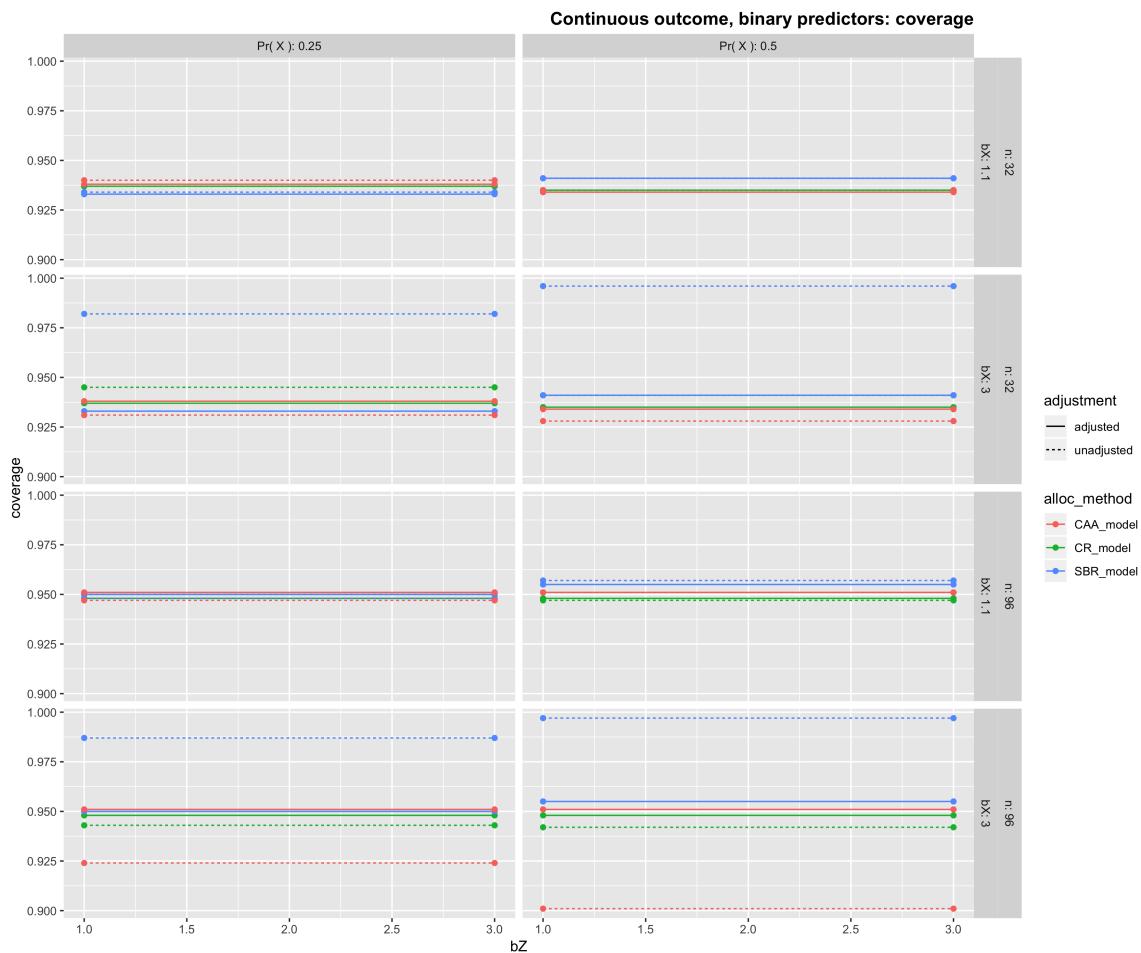


Figure 5.10: Batch 3: Coverage probability

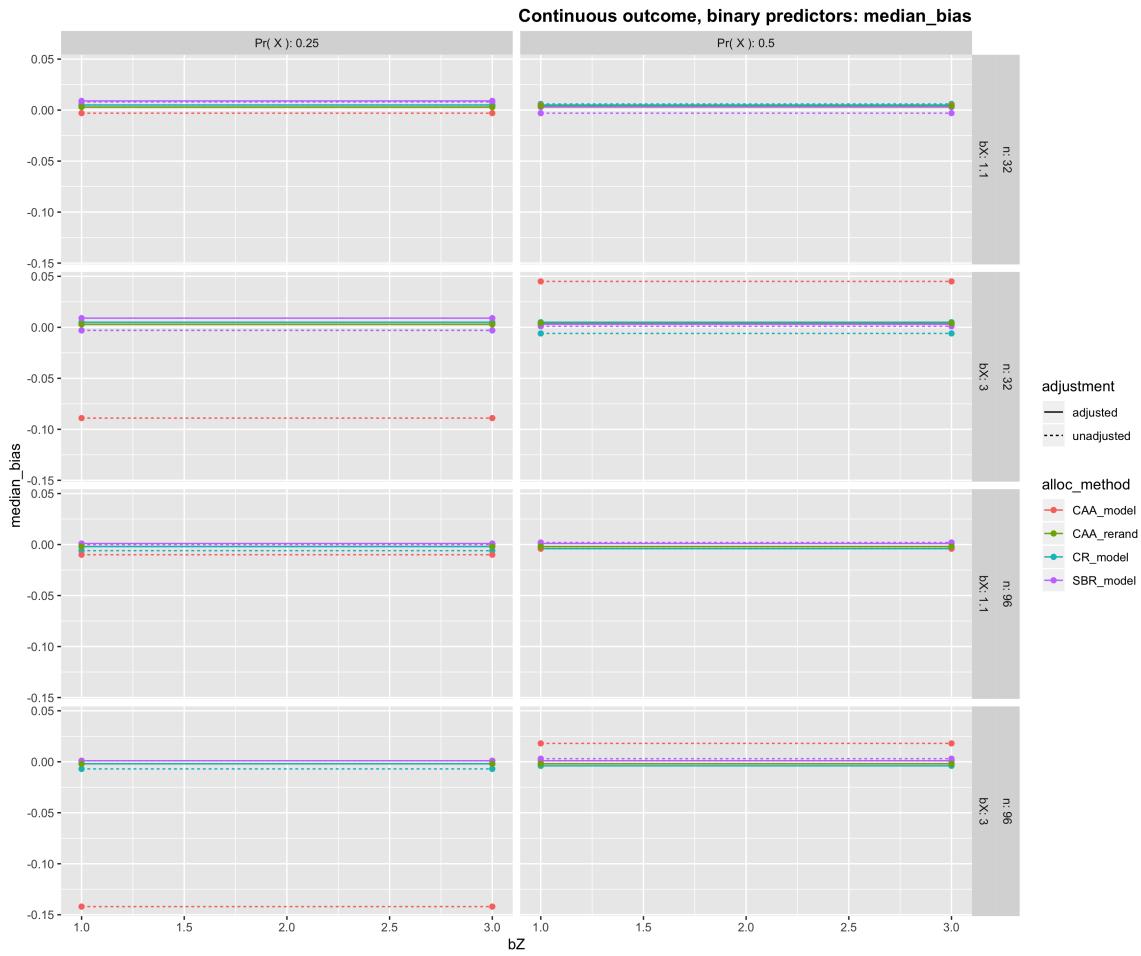


Figure 5.11: Batch 3: Median bias

5.4 Batch 4: Continuous Outcome, Continuous Predictors

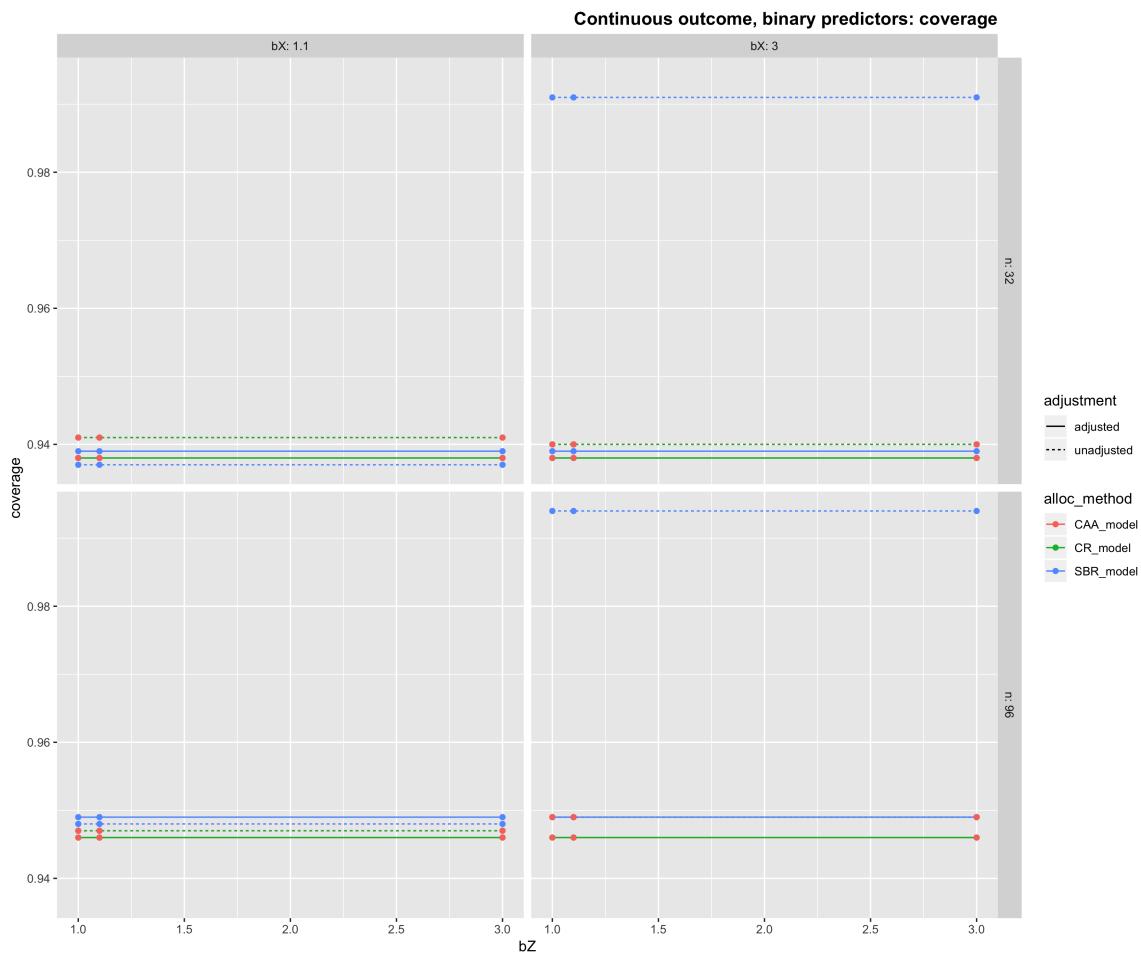


Figure 5.12: Batch 4: Coverage probability

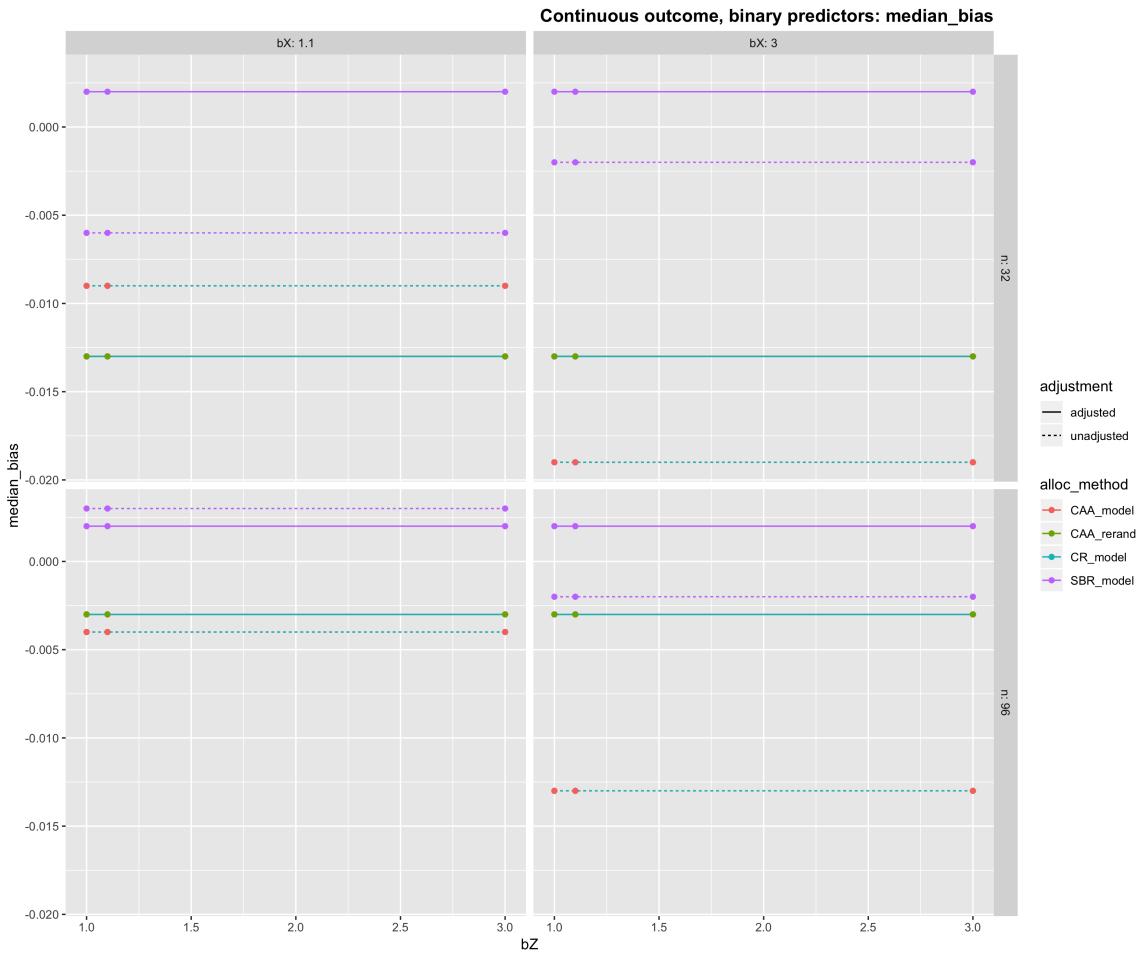


Figure 5.13: Batch 4: Median bias