Impact of Covariate Adaptive Allocation Procedures on Power and Validity in Small-Scale Clinical Studies

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Abstract

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Covariate adaptive allocation presents an attractive alternative to conventional randomization schemes, particularly in small scale clinical studies where balance in multiple prognostic factors is desired. While the approach introduces balance in multiple baseline prognostic factors, the impact on statistical power in various experimental settings compared to complete or restricted randomization is less well understood.

We investigated under which settings covariate adaptive allocation confers a power advantage relative to complete randomization or stratified block randomization. We also considered the impact of statistical adjustment for prognostic factors on power, and sought to address if rerandomization inference under covariate adaptive allocation is appropriate to gain power or to maintain proper type 1 error control.

We conducted a simulation study of a small scale clinical trial of a binary treatment effect and considered both binary and continuous outcomes and prognostic factors. Various trial sizes, treatment and prognostic factor effect sizes, and marginal outcome and prognostic factor prevalences were considered. We compared an extension of the covariate adaptive allocation (CAA) scheme proposed by Heritier et. al (2005) to complete randomization and stratified block randomization on power, type 1 error, bias, and coverage probability.

Adjusting for prognostic factors used in the allocation method consistently increased power under almost all considered settings relative to unadjusted analyses, which tended towards conservative inference.

In binary outcomes, power is higher in CAA followed by rerandomization compared to all other methods, after adjustment for prognostic factors. The power benefit from CAA with rerandomization is most apparent in settings with low trial size (n=32) and low marginal outcome prevalence (Pr(Y)=0.10).

Some type 1 error inflation from CAA with rerandomization is observed in the binary setting; subset analysis suggests size issues may be due to convergence issues with logistic regression under low event rates. Where convergence issues are not present, median bias and coverage probability (for model-based approaches) are appreciably controlled under all considered methods after adjusting for prognostic factors. Power for all methods became comparable to CAA with rerandomization under large trial sizes (n=96) or high marginal outcome prevalence (Pr(Y)=0.50). For continuous outcomes and correctly specified analysis models, there is no appreciable difference in power between the considered allocation methods.

Covariate adaptive allocation controls imbalance for multiple prognostic factors and increases power under some settings.

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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 complete 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 Adaptive randomization

A randomization method is static if 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 Efrons 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 allocation 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. als DBR method to instead 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 (Atkinson 1999). 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 precision. 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 allocation (CAA) followed by standard asymptotic tests yield valid inference, and if so, to quantify the gains in precision relative to complete randomization (SR) or stratified block randomization (SBR). We will compare

Heritiers 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 complete 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 outcome prevalence varies from 10% to 50% in the binary outcome setting, inference on treatment effect is performed adjusting for none or all 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 discuss the

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

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 precision by estimating power as a function of the true treatment effect size.

We evaluate accuracy by estimating any potential bias for all methods. We also estimate coverage probability of confidence intervals for model-based analysis approaches. However, we cannot evaluate coverage probability for permutation test quantile-based confidence intervals as they are estimated under the null hypothesis.

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 (n) 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) and pre-specified prognostic factors (X).

Binary risk factors were simulated such that their marginal prevalence was either 25% or 50%. Continuous risk factors were generated under a standard normal distribution. The prognostic 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 prognostic 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 last subsection entitled 'Re-randomization inference').

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,[1] and an adapted form of covariate adaptive allocation proposed by Heritier et. al (2005).

For the covariate adaptive allocation 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 allocations on inference.

2.3 Varied conditions

The following table describes the conditions varied in the binary outcome setting.

Table 2.1: Simulation study conditions

Variable (notation)	Description	Associated parameters	Cardinality
Response (Y)	Outcome, binary or continuous	Marginal prevalence $p_Y \equiv Pr(Y=1) = \{0.1, 0.5\}$	2 dichotomous, 1 continuous = 3
Treatment assignment (Z)	$Z = \{0, 1\}$	$p_{alloc} \equiv Pr(Z=1) = 0.5$	1
Prognostic factors (X)	Binary: $X = \{0, 1\}$ Continuous: dichotomized by pop. median	$p_X \equiv Pr(X=1) = \{0.25, 0.5\}$	2 dichotomous, 1 continuous = 3
Trial size (n)	Overall sample size	$n = \{32, 96\}$	2
Effect sizes (β_X and β_Z)[2]	$\beta = \begin{cases} \text{None:} & \exp(\beta) = 1 \\ \text{Low:} & \exp(\beta) = 1.1 \\ \text{High:} & \exp(\beta) = 3 \end{cases}$	$\beta_Z = \{log(1.0), log(1.1), log(3)\}$ $\beta_X = \{log(1.1), log(3)\}$	3*2 = 6

[1] Block sizes are equal to overall trial size divided by number of strata, which are defined by all combinations of balancing factor levels.

[2] 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 prognostic factors. To evaluate power, coverage, and type I error control, we report the associated linear and logistic regression model-based p-values and Wald-type confidence intervals, based on a two-sided type I error threshold of 0.05. For balancing purposes, continuous prognostic factors were first dichotomized by their population median, and later parameterized as continuous in the adjusted analysis.

The simulation model is of the form

$$g(E[Y_i|Z_i, \mathbf{X}_i]) = \beta_0 + \beta_Z \cdot Z_i + \beta_X \cdot \mathbf{X}_i. \tag{2.1}$$

the adjusted regression model is,

$$g(E[Y_i|Z_i, \mathbf{X}_i]) = \beta_0 + \beta_Z \cdot Z_i + \beta_X \cdot \mathbf{X}_i, \tag{2.2}$$

and the unadjusted model is

$$g(E[Y_i|Z_i]) = \gamma_0 + \gamma_Z \cdot Z_i, \tag{2.3}$$

where $g()$ is the identity link when Y is continuous and the logit link when Y is binary.

Re-randomization inference

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 allocation. 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, prognostic factors, and observed entry

time 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 5,000 trials, for which the re-randomization procedure was repeated 500 times.

3 Simulation

For each batch of simulations defined by outcome and predictor variable type, the following tables report power, median bias, and coverage probability.

Tables are included in this section 'Simulation', and results are described and summarized in the subsequent section entitled 'Results'. Tables of results are displayed by trial size (n), marginal outcome prevalence ($Pr(Y)$) when the outcome is binary, prognostic factor prevalence ($Pr(X)$) when prognostic factors are binary, treatment effect size (bZ), and prognostic factor effect size (bX).

Results are reported separately by model adjustment for prognostic factors, the treatment allocation method used (CR - complete randomization, SBR - stratified block randomization, CAA: covariate adaptive allocation[1]), and analysis type (model-based or rerandomization).

For the batches where binary outcomes are considered, power is reported averaging over the subset of simulation results where the `glm` algorithm converged and at least one event was observed in each treatment arm.

[1]see Section 2.2: *Allocation procedures* for method parameters and implementation details

3.1 Batch 1: Binary Outcome, Binary Predictors

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

					Model-based						Rerandomization
					CR		SBR		CAA		CAA
n	Pr(Y)	Pr(X)	bZ	bX	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

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

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

					Model-based					
					CR		SBR		CAA	
n	Pr(Y)	Pr(X)	bZ	bX	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

Table 3.4: Batch 1 (Binary Y, Binary X): Power, subsetted

						Model-based						Rerandomization
						CR		SBR		CAA		CAA
Avg. nsims	n	Pr(Y)	Pr(X)	bZ	bX	adj	unadj	adj	unadj	adj	unadj	adj
3452 (68.9%)	32	0.1	0.25	1.0	1.1	0.006	0.001	0.003	0.000	0.003	0.001	0.017
3818 (76.2%)	32	0.1	0.25	1.0	3.0	0.008	0.001	0.007	0.000	0.009	0.001	0.025
3451 (68.9%)	32	0.1	0.25	1.1	1.1	0.007	0.001	0.003	0.000	0.003	0.000	0.017
3804 (75.9%)	32	0.1	0.25	1.1	3.0	0.008	0.001	0.008	0.001	0.010	0.001	0.024
3062 (61.1%)	32	0.1	0.25	3.0	1.1	0.018	0.007	0.012	0.005	0.012	0.005	0.044
3408 (68%)	32	0.1	0.25	3.0	3.0	0.024	0.010	0.022	0.006	0.025	0.010	0.065
3445 (68.8%)	32	0.1	0.50	1.0	1.1	0.009	0.001	0.009	0.000	0.005	0.000	0.021
3868 (77.2%)	32	0.1	0.50	1.0	3.0	0.021	0.002	0.025	0.001	0.022	0.001	0.022
3443 (68.7%)	32	0.1	0.50	1.1	1.1	0.009	0.001	0.008	0.001	0.004	0.000	0.021
3879 (77.4%)	32	0.1	0.50	1.1	3.0	0.021	0.002	0.024	0.001	0.024	0.001	0.022
3053 (60.9%)	32	0.1	0.50	3.0	1.1	0.019	0.007	0.013	0.003	0.018	0.006	0.046
3482 (69.5%)	32	0.1	0.50	3.0	3.0	0.055	0.010	0.052	0.004	0.057	0.009	0.068
5008 (100%)	32	0.5	0.25	1.0	1.1	0.028	0.029	0.031	0.026	0.028	0.025	0.057
5009 (100%)	32	0.5	0.25	1.0	3.0	0.019	0.023	0.022	0.017	0.025	0.022	0.056
5009 (100%)	32	0.5	0.25	1.1	1.1	0.025	0.027	0.027	0.022	0.033	0.029	0.063
5009 (100%)	32	0.5	0.25	1.1	3.0	0.023	0.025	0.024	0.017	0.026	0.022	0.059
5001 (99.8%)	32	0.5	0.25	3.0	1.1	0.210	0.231	0.232	0.230	0.222	0.219	0.326
5001 (99.8%)	32	0.5	0.25	3.0	3.0	0.173	0.192	0.197	0.182	0.199	0.182	0.301
5008 (100%)	32	0.5	0.50	1.0	1.1	0.026	0.029	0.026	0.025	0.026	0.025	0.062
5009 (100%)	32	0.5	0.50	1.0	3.0	0.022	0.025	0.028	0.016	0.024	0.019	0.059
5009 (100%)	32	0.5	0.50	1.1	1.1	0.029	0.030	0.024	0.023	0.024	0.023	0.064
5009 (100%)	32	0.5	0.50	1.1	3.0	0.027	0.031	0.028	0.018	0.028	0.022	0.061
5000 (99.8%)	32	0.5	0.50	3.0	1.1	0.203	0.227	0.223	0.224	0.223	0.228	0.326
5004 (99.9%)	32	0.5	0.50	3.0	3.0	0.161	0.177	0.190	0.164	0.180	0.170	0.299
4944 (98.7%)	96	0.1	0.25	1.0	1.1	0.026	0.018	0.024	0.019	0.026	0.018	0.050
4985 (99.5%)	96	0.1	0.25	1.0	3.0	0.039	0.026	0.041	0.026	0.036	0.019	0.049
4939 (98.6%)	96	0.1	0.25	1.1	1.1	0.026	0.019	0.027	0.020	0.028	0.018	0.054
4983 (99.5%)	96	0.1	0.25	1.1	3.0	0.038	0.027	0.040	0.025	0.039	0.022	0.052
4726 (94.3%)	96	0.1	0.25	3.0	1.1	0.238	0.222	0.227	0.218	0.238	0.220	0.324
4877 (97.3%)	96	0.1	0.25	3.0	3.0	0.277	0.252	0.282	0.248	0.285	0.248	0.360
4950 (98.8%)	96	0.1	0.50	1.0	1.1	0.024	0.018	0.025	0.017	0.027	0.018	0.053
4992 (99.6%)	96	0.1	0.50	1.0	3.0	0.045	0.024	0.044	0.021	0.048	0.026	0.058
4947 (98.7%)	96	0.1	0.50	1.1	1.1	0.025	0.019	0.023	0.018	0.027	0.019	0.054
4991 (99.6%)	96	0.1	0.50	1.1	3.0	0.047	0.026	0.045	0.021	0.049	0.025	0.057

4752 (94.9%)	96	0.1	0.50	3.0	1.1	0.230	0.224	0.231	0.218	0.244	0.230	0.334
4899 (97.8%)	96	0.1	0.50	3.0	3.0	0.316	0.274	0.334	0.282	0.325	0.273	0.381
5010 (100%)	96	0.5	0.25	1.0	1.1	0.043	0.045	0.044	0.048	0.038	0.045	0.050
5010 (100%)	96	0.5	0.25	1.0	3.0	0.046	0.047	0.045	0.041	0.043	0.041	0.055
5010 (100%)	96	0.5	0.25	1.1	1.1	0.046	0.049	0.049	0.052	0.046	0.052	0.057
5010 (100%)	96	0.5	0.25	1.1	3.0	0.050	0.051	0.051	0.048	0.048	0.047	0.060
5010 (100%)	96	0.5	0.25	3.0	1.1	0.725	0.744	0.730	0.745	0.741	0.764	0.752
5010 (100%)	96	0.5	0.25	3.0	3.0	0.680	0.649	0.691	0.675	0.683	0.672	0.704
5010 (100%)	96	0.5	0.50	1.0	1.1	0.044	0.047	0.045	0.050	0.048	0.053	0.059
5010 (100%)	96	0.5	0.50	1.0	3.0	0.042	0.048	0.042	0.036	0.046	0.044	0.058
5010 (100%)	96	0.5	0.50	1.1	1.1	0.045	0.047	0.049	0.054	0.050	0.056	0.059
5010 (100%)	96	0.5	0.50	1.1	3.0	0.046	0.048	0.047	0.042	0.046	0.040	0.057
5010 (100%)	96	0.5	0.50	3.0	1.1	0.725	0.741	0.740	0.757	0.739	0.758	0.752
5010 (100%)	96	0.5	0.50	3.0	3.0	0.661	0.629	0.676	0.647	0.669	0.648	0.694

3.2 Batch 2: Binary Outcome, Continuous Predictors

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

				Model-based						Rerandomization
				CR		SBR		CAA		CAA
n	Pr(Y)	bZ	bX	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 3.6: Batch 2 (Binary Y, Continuous X): Median bias

				Model-based						Rerandomization
				CR		SBR		CAA		CAA
n	Pr(Y)	bZ	bX	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 3.7: Batch 2 (Binary Y, Continuous X): Coverage probability

				Model-based					
				CR		SBR		CAA	
n	Pr(Y)	bZ	bX	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 3.8: Batch 2 (Binary Y, Continuous X): Power, subsetted

					Model-based						Rerandomization
					CR		SBR		CAA		CAA
Avg. nsims	n	Pr(Y)	bZ	bX	adj	unadj	adj	unadj	adj	unadj	adj
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 3.9: Batch 3 (Continuous Y, Binary X): Power

				Model-based						Rerandomization
				CR		SBR		CAA		CAA
n	Pr(X)	bZ	bX	adj	unadj	adj	unadj	adj	unadj	adj
32	0.25	1	1.1	0.053	0.052	0.055	0.056	0.053	0.050	0.060
32	0.25	1	3.0	0.053	0.046	0.055	0.013	0.053	0.059	0.060
32	0.25	3	1.1	0.999	1.000	0.999	0.999	0.997	0.999	0.903
32	0.25	3	3.0	0.999	0.930	0.999	0.970	0.997	0.876	0.903
32	0.50	1	1.1	0.053	0.055	0.048	0.051	0.054	0.053	0.061
32	0.50	1	3.0	0.053	0.051	0.048	0.003	0.054	0.061	0.061
32	0.50	3	1.1	0.999	0.999	1.000	1.000	0.999	0.999	0.996
32	0.50	3	3.0	0.999	0.870	1.000	0.957	0.999	0.879	0.996
96	0.25	1	1.1	0.049	0.047	0.047	0.047	0.047	0.049	0.032
96	0.25	1	3.0	0.049	0.053	0.047	0.011	0.047	0.074	0.032
96	0.25	3	1.1	1.000	1.000	1.000	1.000	1.000	1.000	0.995
96	0.25	3	3.0	1.000	1.000	1.000	1.000	1.000	0.999	0.995
96	0.50	1	1.1	0.048	0.049	0.042	0.040	0.045	0.046	0.057
96	0.50	1	3.0	0.048	0.054	0.042	0.002	0.045	0.095	0.057
96	0.50	3	1.1	1.000	1.000	1.000	1.000	1.000	1.000	1.000
96	0.50	3	3.0	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 3.10: Batch 3 (Continuous Y, Binary X): Median bias

				Model-based						Rerandomization
				CR		SBR		CAA		CAA
n	Pr(X)	bZ	bX	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	0.002	-0.002	-0.004	-0.002
96	0.50	3	3.0	-0.004	0.001	0.001	0.003	-0.002	0.018	-0.002

Table 3.11: Batch 3 (Continuous Y, Binary X): Coverage probability

				Model-based					
				CR		SBR		CAA	
n	Pr(X)	bZ	bX	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 3.12: Batch 4 (Continuous Y, Continuous X): Power

			Model-based						Rerandomization
			CR		SBR		CAA		CAA
n	bZ	bX	adj	unadj	adj	unadj	adj	unadj	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 3.13: Batch 4 (Continuous Y, Continuous X): Median bias

			Model-based						Rerandomization
			CR		SBR		CAA		CAA
n	bZ	bX	adj	unadj	adj	unadj	adj	unadj	adj
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 3.14: Batch 4 (Continuous Y, Continuous X): Coverage probability

			Model-based					
			CR		SBR		CAA	
n	bZ	bX	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

3.5 Figures: Power, all settings

The figures below present power curves from the previously reported tables for comparing between methods and simulation conditions.

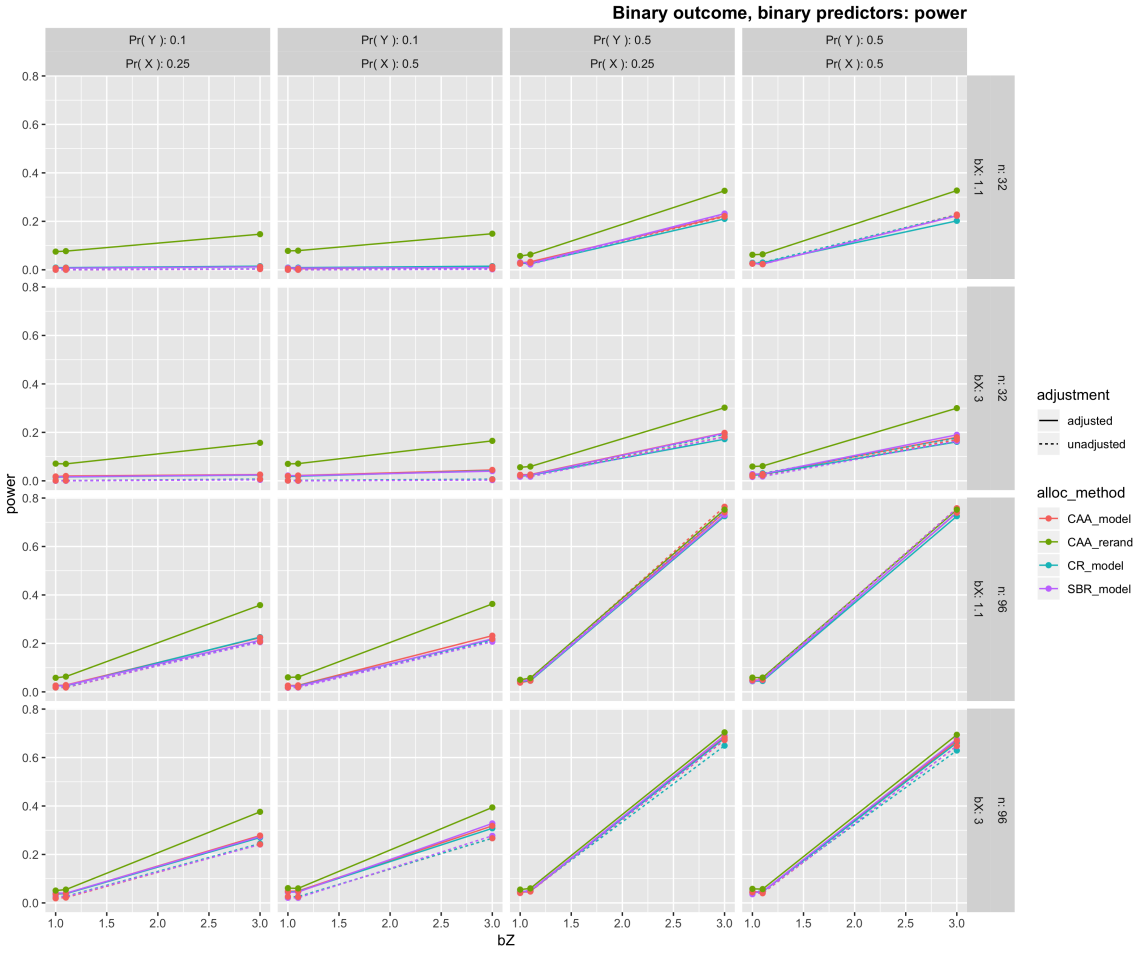

Figure 3.1: Batch 1: Power

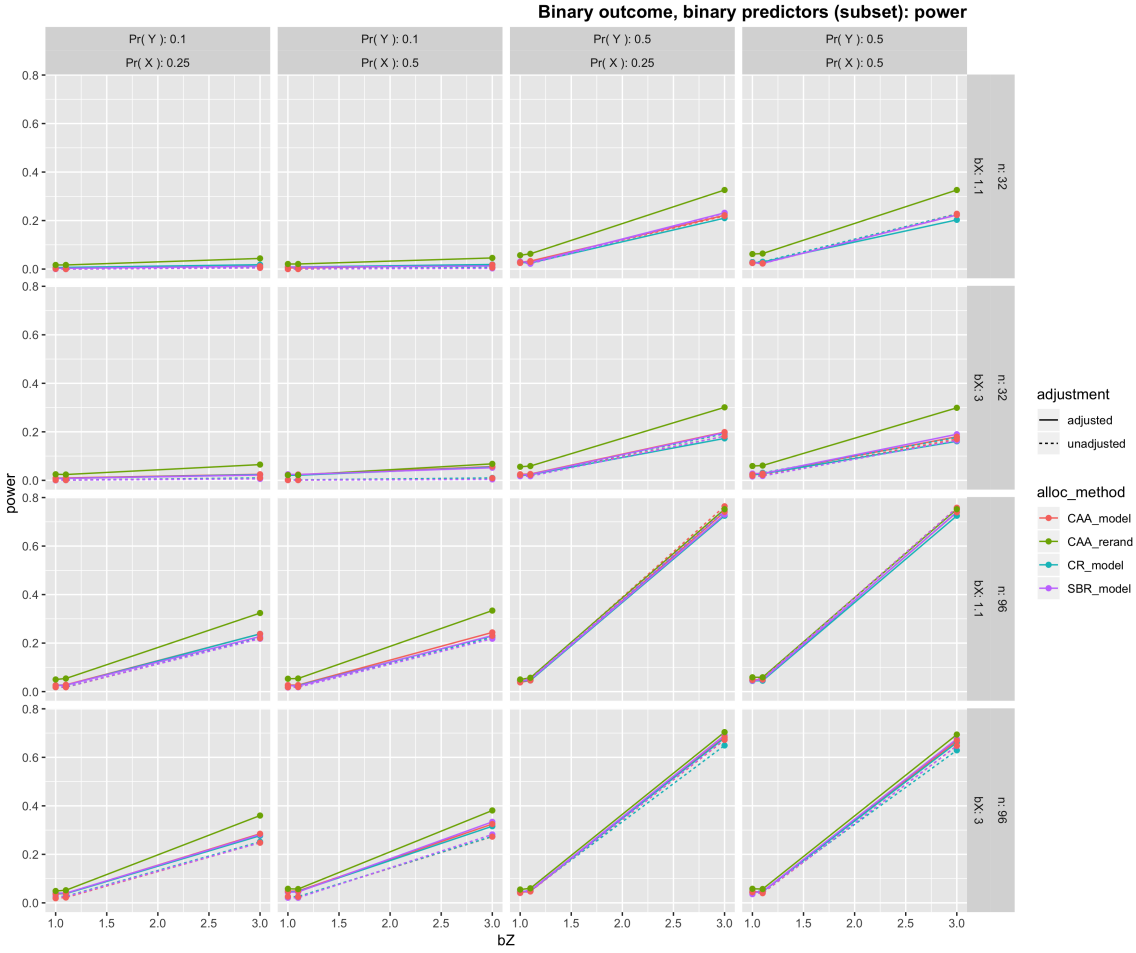

Figure 3.2: Batch 1 subset: Power

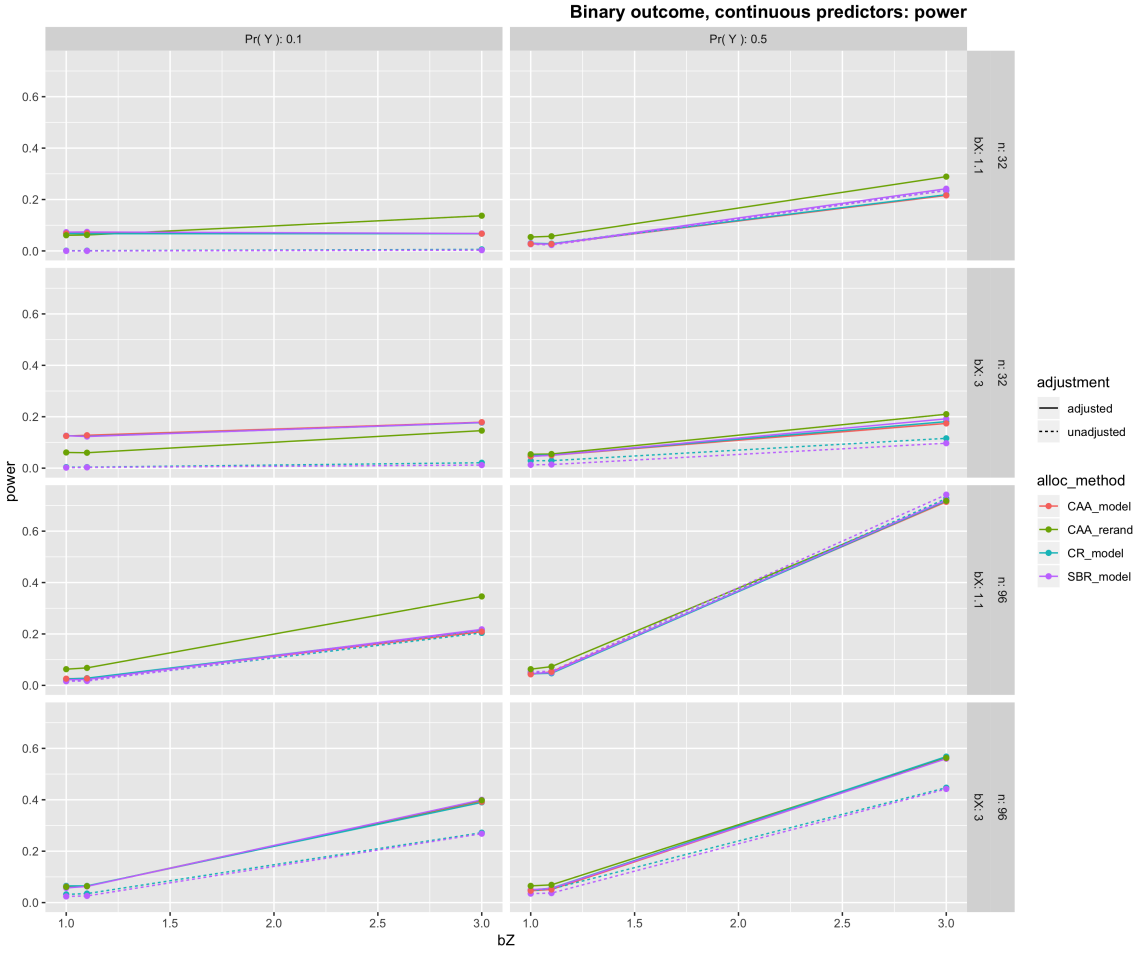

Figure 3.3: Batch 2: Power

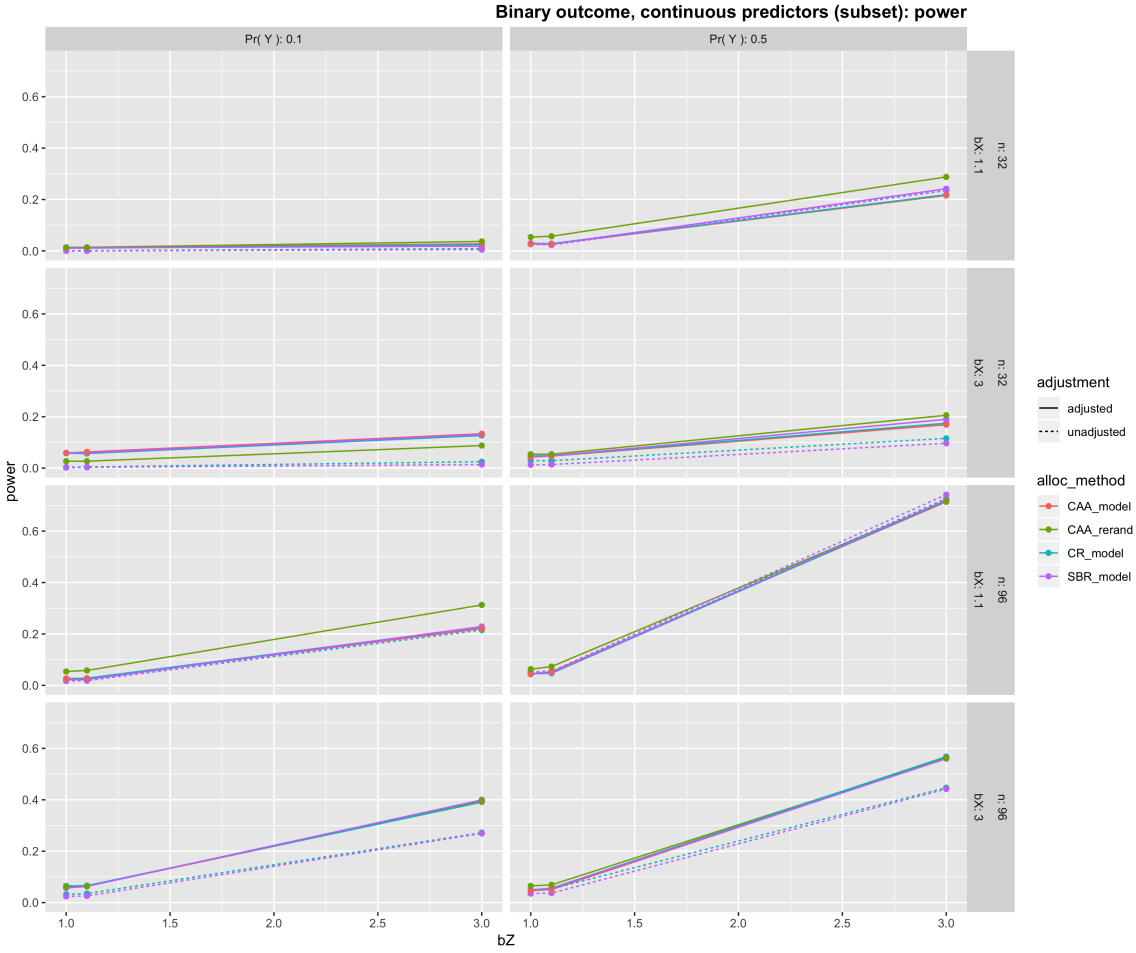

Figure 3.4: Batch 2 subset: Power

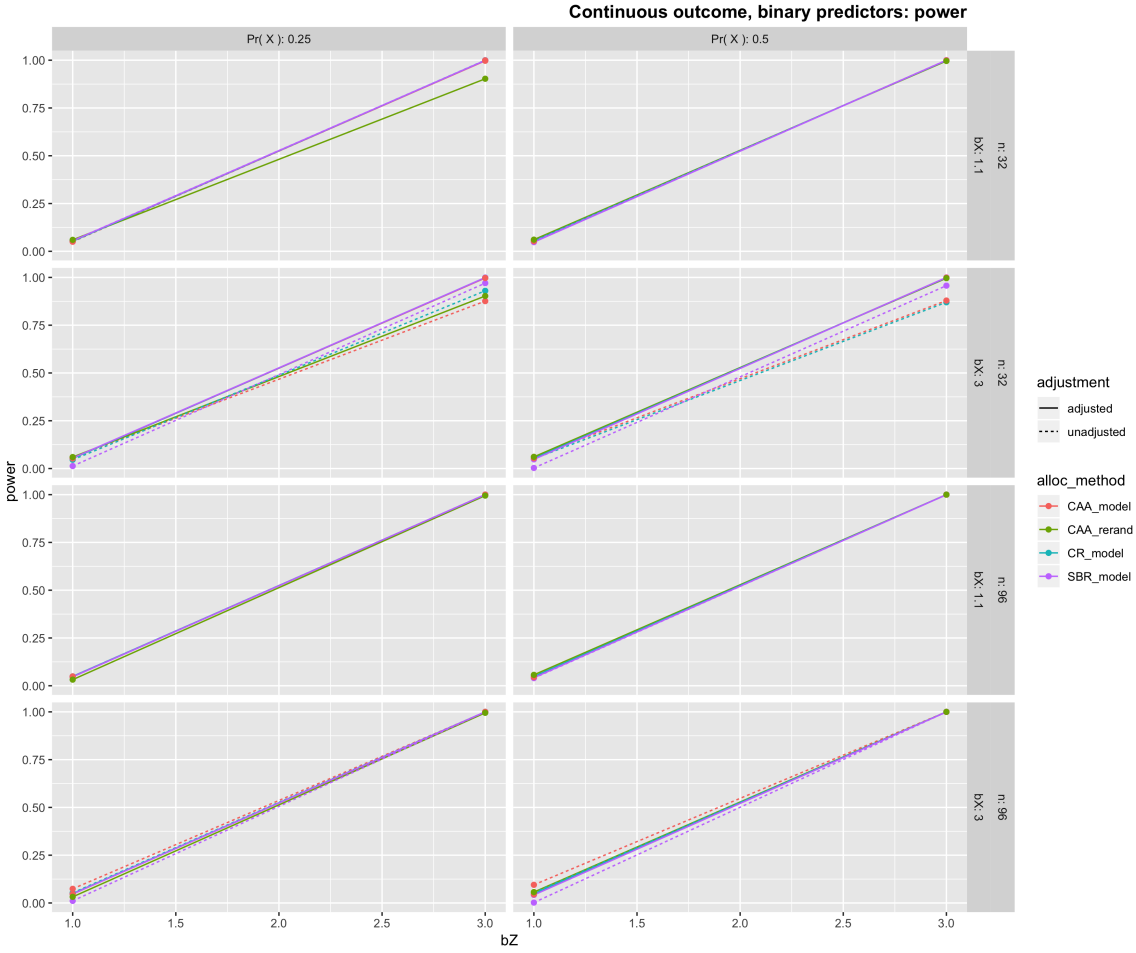

Figure 3.5: Batch 3: Power

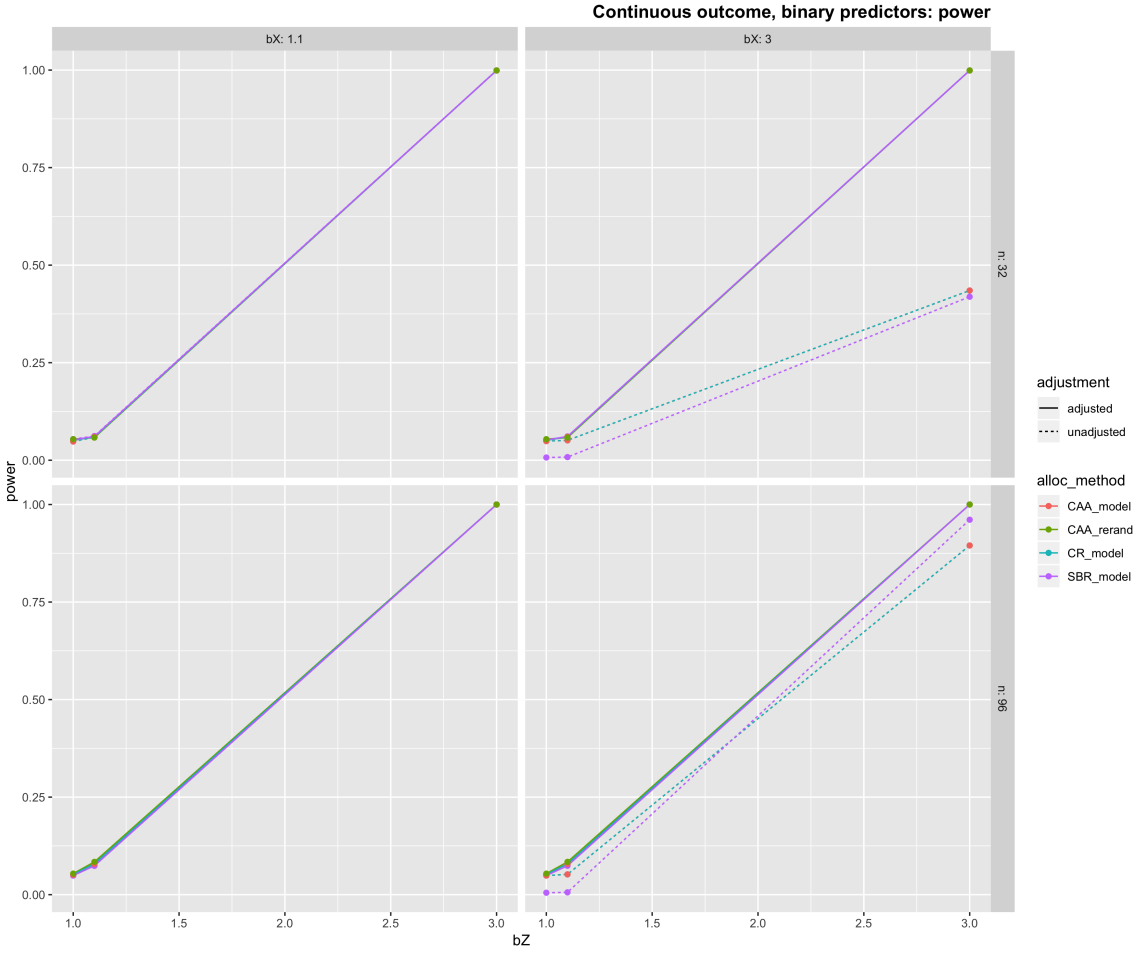

Figure 3.6: Batch 4: Power

4 Results

4.1 Binary outcome setting

Note on subsetted simulations

Simulations with low observed event rates in the binary outcome model could result in large estimated treatment effects and standard errors, 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 event was observed in each treatment arm. Subsetting on these two criterion led to excluding greater than 30 percent of simulations in low sample size scenarios. This issue occurs more frequently 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).

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 especially apparent in low sample size settings and low marginal outcome prevalence, although the increased power is in part due to the inflated Type 1 error (see Table 3.1 rows 1 and 2). The size issues with re-randomization occur only in specific settings, particularly where convergence issues with logistic regression are present. Not all gains in power for CAA with re-randomization are due to Type 1 error inflation: when outcome prevalence increases to 50% from 10%, the type 1 error rate is 0.057 and 0.056 and approaches the nominal rate (see Table 3.1 Rows 13, 14) while power in all considered non-null effect sizes is consistently greater than the other methods.

Adjusting for prognostic factors used in the balancing method consistently in-

creased power relative to unadjusted methods in almost all considered settings. Evidence that unadjusted model-based regression approaches are too conservative is seen when comparing size of the tests for the binary outcome setting and the continuous outcome setting when using SBR with high prognostic factor effect size. For example, see Table 3.5 for n=96, $(Pr(Y)) = 0.1$, $bZ = 1$ and $bX = 3$ for complete randomization: size of the unadjusted test is .032 and adjusted is .065. Similarly see Table 3.9 for continuous outcomes where n=96, $(Pr(X)) = 0.25$, $bZ = 1$ and $bX = 3$, size for SBR is .011 unadjusted an .047 after adjusting. Comparing model-based approaches, adjustment for prognostic factors was necessary to maintain proper Type 1 error control and to maximize power under almost all considered settings and outcome types. The power advantage of adjusted relative to unadjusted analysis generally increases with prognostic factor effect sizes.

The power benefit from using CAA followed by re-randomization becomes diminished relative to all other allocation procedures an analytic methods when sample size increases and marginal outcome prevalence increases (see Figure 3.1, bottom right quadrant). Even at large sample sizes re-randomization has greater power than model-based approaches, particularly when outcome prevalence is low.

Median bias (Table 3.2) is appreciably low and approaches zero when the estimated treatment effect is null or when trial size is large (n=96). The bias results from glm() algorithm returning inflated estimates when no valid odds ratio estimate exists, *i.e.* when the denominator of the odds ratio is zero because there are no events in the untreated arm. This happens more often when considering within-strata odds ratios, which is why the median bias for adjusted estimates, though still small, is larger on average when compared to unadjusted estimates.

Coverage probability nears 100 percent at low outcome prevalence and low trial size, likely from standard errors being too large with low event rates. Coverage

probability nears 95 percent when outcome prevalence is high and when sample size is large (n=96).

Recall that subsetted results included only simulations where the algorithm converged and at least one event was observed in each treatment arm. Compared to results on all simulations, subsetted power results show better type I error control for CAA followed by re-randomization overall (compare Table 3.1 rows 1,2 with Table 3.4, rows 1,2). The modest power increase of CAA with re-randomization relative to other allocation procedures using model-based analysis is consistent in large and small sample sizes and high and low outcome prevalences.

Continuous predictors

Both CAA and SBR with model-based inference have the highest power compared to all other approaches but fail to control size. In low outcome prevalence (Pr(Y)=0.1) under strong prognostic factor effect size (bX=3) with a type I error threshold of 0.05, the power under the null setting is greater than 0.10 (see Table 3.5, rows 1,2). As discussed in the previous section, the tendency for `glm()` to return large estimates and standard errors given certain simulation outcomes results in spuriously small p-values. Looking at the subsetted results in Table 3.8 where size is at least as well controlled for re-randomization as other methods, power is highest with re-randomization or at least comparable to model-based approaches that adjust for prognostic factors.

Considering model-based approaches, adjusted estimates are consistently more powerful than unadjusted estimates. Adjusting for prognostic factors used in the balancing method controls median bias. Median bias tended to be less than 10 percent and decreased with increasing sample size.

The coverage probability at low sample sizes was inflated due to low event rates, as described in the previous section on binary predictors. All adjusted methods have

coverage probabilities near 95 percent in the large sample size setting.

4.2 Continuous outcome setting

Binary predictors

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

Median bias was tiny and coverage probability approached 95 percent for all methods and all conditions. An exception is when prognostic factor effect size is large, stratified block randomization was used, and covariates were not adjusted for: see for example Table 3.10, even rows.

Continuous predictors

Adjusting for prognostic factors did not considerably increase power, except when prognostic factor effect size is large. As in all simulated conditions with a continuous outcome, re-randomization following allocation does not confer an additional advantage in terms of increased power.

5 Discussion

5.1 Discussion

We sought to address whether covariate-adaptive allocation followed by re-randomization conferred any statistical power advantage relative to complete randomization, stratified block randomization, and covariate-adaptive allocation using model-based inference. By simulating both binary and continuous outcomes and prognostic factors, our study considered a broad range of settings compared to previous work.

We specified the models correctly as simulated. As mentioned in the previous section on subsetted simulations, coverage probability and bias were inflated due to low event rates and their corresponding effect on logistic regression model output. Our simulation exclusion criteria is similar to Kalish and Begg (1987) which excluded any analysis with a singular design matrix or if any response by treatment count was zero. All issues with coverage or bias were ameliorated after requiring sufficient events for convergence, either by subsetting on previously mentioned criterion or increasing trial size. When either the outcome prevalence or trial size was increased, bias approached zero and coverage probability converged to the nominal rate. Size was also well controlled when convergence was not an issue.

Re-randomization inference tends to be more powerful relative to model-based analysis for selected conditions, particularly for binary outcomes where the marginal outcome prevalence or overall trial size is low. Similarly, not adjusting for prognostic factors resulted in more conservative inference regardless of the allocation method used. Our findings match the consensus that ignoring prognostic factors used in allocation scheme leads to conservative inference (Forsythe 1985, Kalish and Begg 1987, Scott et. al 2002, Shao 2010, Ma 2015). Adjusting for prognostic factors used in the allocation procedure in linear models was also found necessary to obtain proper size by Birkett (1985), Forsythe (1987), and Lachin, Matts, Wei (1988).

Previous study on the use of rerandomization analysis states while it is often not adopted because of its computational complexity, it remains a useful alternative to model-based inference when drift is present or when implementing covariate adaptive allocation methods with greater degrees of deterministic allocations. Simon (1979) state the importance of using such approaches for calculating the appropriate randomization significance level to obtain the full benefit of the power gain with such adaptive procedures (Birkett 1985). Model-based analysis assumes a time homogeneous population with respect to the outcome measure, which may not always be satisfied in practice (Lachin, Matts, Wei 1988) Scott (2002), Browne et. al (2005), and Simon and Simon (2011) recommend rerandomization analysis to protect against type 1 error inflation if there may be time trends in the outcome measure independent of the measured prognostic factors. For survival outcomes, Xu et. al (2016) found rerandomization to be just as powerful as the stratified log-rank test for estimating adjusted treatment effect hazard ratios.

One limitation of our study is that our simulation considered a fixed number of independent prognostic factors. To compare stratification with CAA under realistic use cases, we could have additionally considered settings with multiple (potentially correlated) prognostic factors, where it would be infeasible to include all baseline variables in stratified allocation. Several authors (Birkett 1987, Scott et. al 2002) suggest that these settings are where minimization outperforms stratification.

In the continuous prognostic factor settings, we also only considered Normally distributed random variables and dichotomized them by their median for determinining groups for balanced allocations. The general consensus is to incorporate balancing variables into the analysis 'as-is'; however in our simulations the dichotomized variables were used for blocking and adaptive allocation and the continuous measure used in the analysis. Future methods could consider using an approach of balancing means

of prognostic variables across treatment groups, in order to leverage additional information lost by dichotomizing continuous prognostic variables by arbitrary cutpoints. Aickin (1998, 2002, 2009) proposed a method for balancing continuous covariates; they were not considered since they require specifying a model between outcome and prognostic factors for the allocation procedure.

Another limitation of our findings is how we did not explicitly model drift, or a change in the outcome prevalence over time that is unrelated to measured prognostic variables. Not accounting for drift could lead to potential bias (Scott 2002, Brown et. al 2005, and Simon and Simon 2011). This phenomenon is often encountered in practice and is a major consideration for adopting stratification or covariate adaptive allocation methods. Several authors (Halpern and Brown 1986, Green, McEntegart, Byrom, Ghani, Shepherd 2001) claim that classical (model-based) analysis yields similar conclusions to rerandomization except in specific circumstances such as drift. Future simulations modeling drift in these settings could potentially assess the relative performance of stratified block randomization and CAA relative to complete randomization for controlling the effects of drift.

There are yet undescribed reasons to consider implementing covariate adaptive allocation with re-randomization as a design and analytic tool. Covariate adaptive allocation procedures are designed to induce balance in prognostic factors, particularly to hedge against chance imbalances that could be seen as compromising the impact of study results. Heritier et. al (2005) note having more homogeneous subgroups does not necessarily yield more efficient inference outside linear regression. However, if subgroup analysis is an important endpoint then allocation procedures ensuring balanced treatment allocations within strata can be useful to facilitate and maximize power for subset analyses (Lachin, Matts, Wei 1988, Emerson 2010).

Using covariate adaptive allocation procedures to control imbalance involves es-

chewing the benefits of complete randomization in permitting straightforward analysis and interpretation of results. Complete randomization allows for population model-based analysis, circumventing the need for implementing permutation model-based analysis to obtain proper size. Permutation model-based analysis can only generate confidence intervals under the null hypothesis (Emerson 2010), and require bootstrap or other resampling techniques to generate confidence intervals for parameter estimates (Ma 2015).

5.2 Conclusions

We have identified conditions under which covariate adaptive allocation followed by rerandomization analysis provides additional power advantages over adjusted model-based methods. The degree to which pre-randomization stratification and adjustment in the analysis addresses the issues presented by chance imbalance in potential confounding factors is still debated. When considering between complete or restricted randomization and covariate adaptive allocation methods, careful thought is recommended to identify relevant baseline covariates and to weigh their relative importance for strict balance. While there may be a modest increase in power from covariate adaptive allocation in some settings, it comes with the potential for added complexity in the analysis and must be implemented judiciously.

6 Figures

6.1 Batch 1: Binary Outcome, Binary Predictors

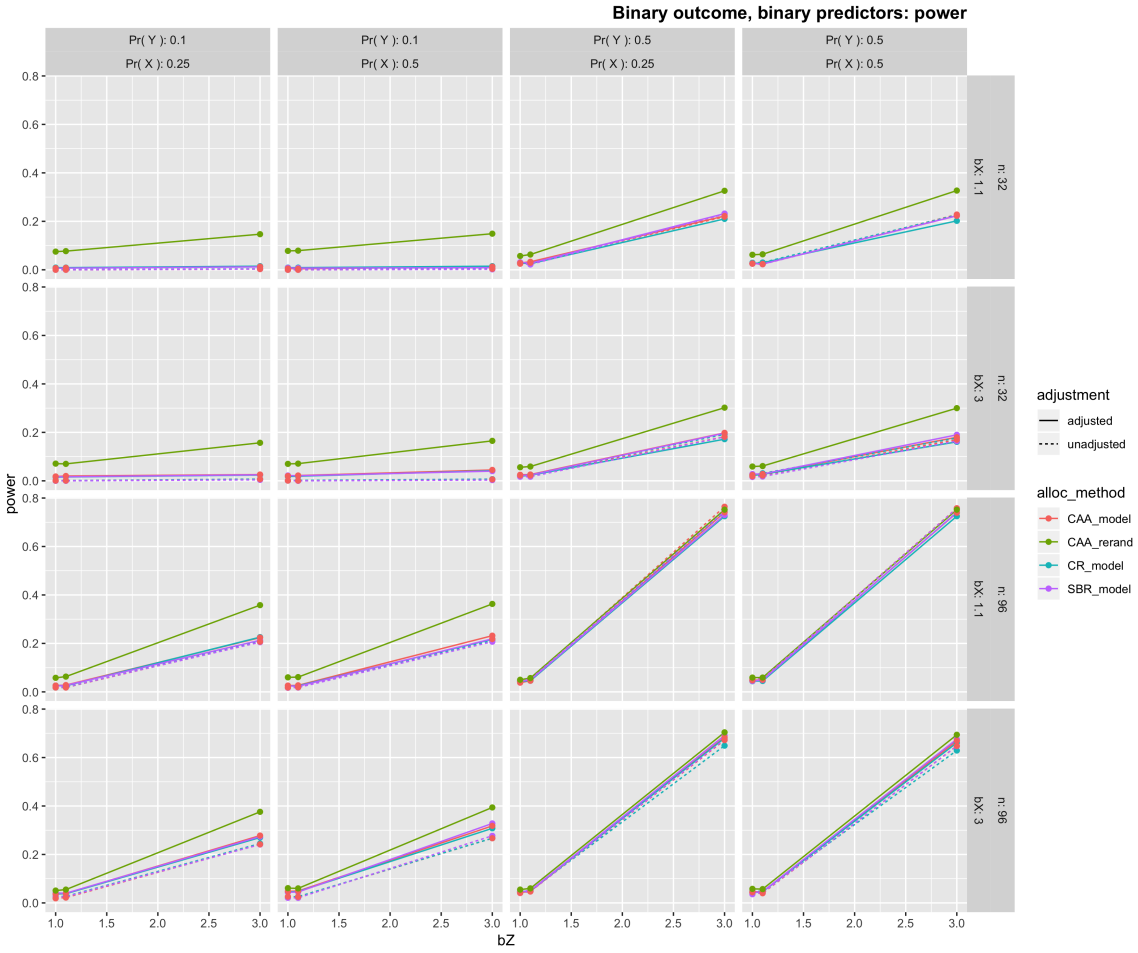

Figure 6.1: Batch 1: Power

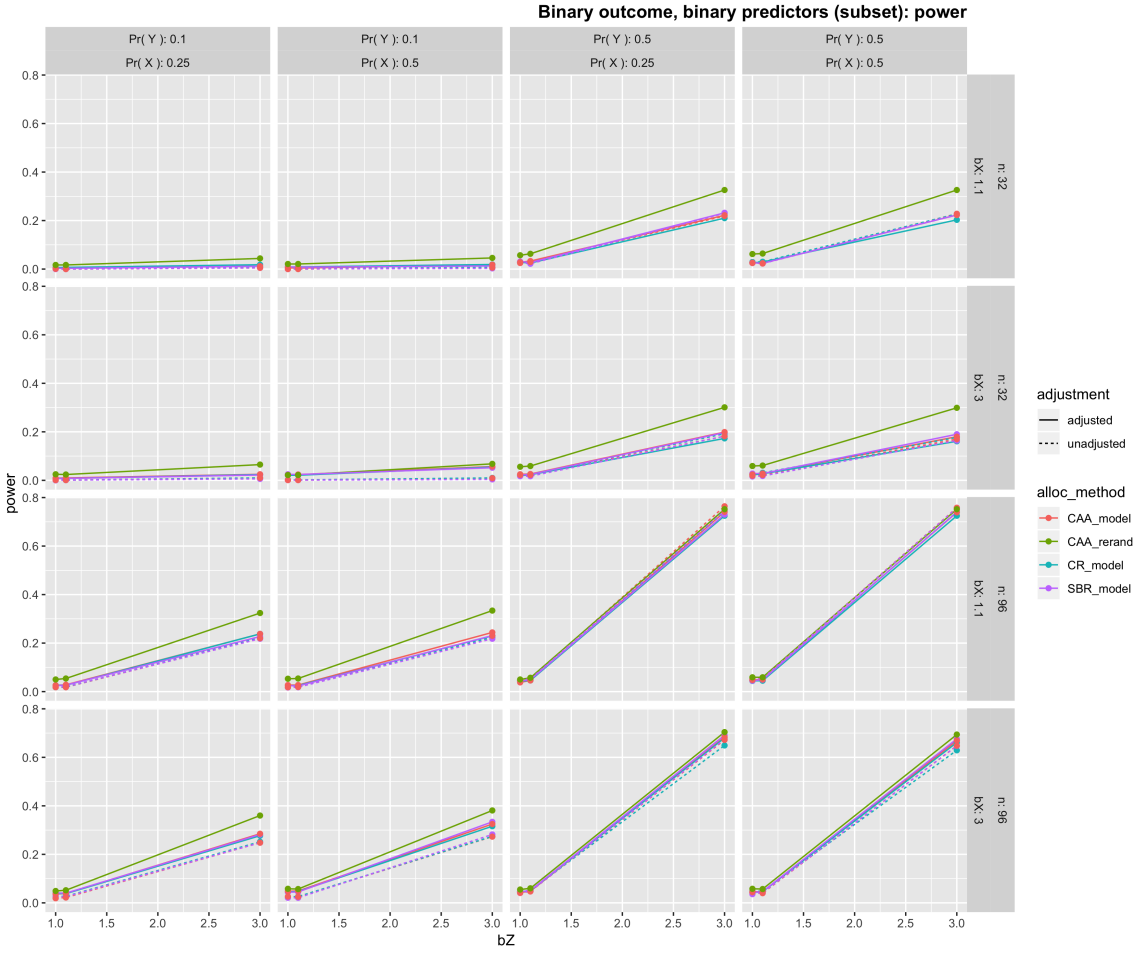

Figure 6.2: Batch 1 subset: Power

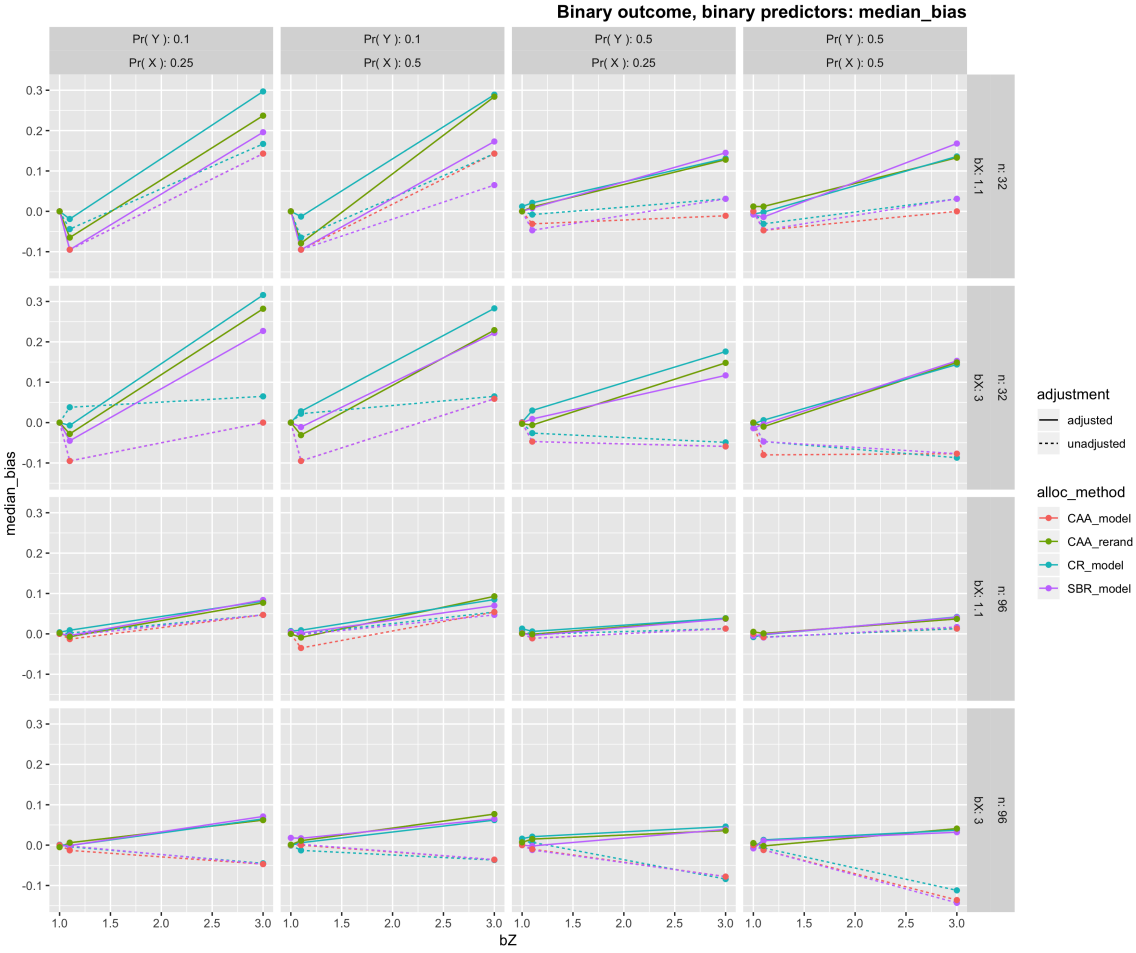

Figure 6.3: Batch 1: Median bias

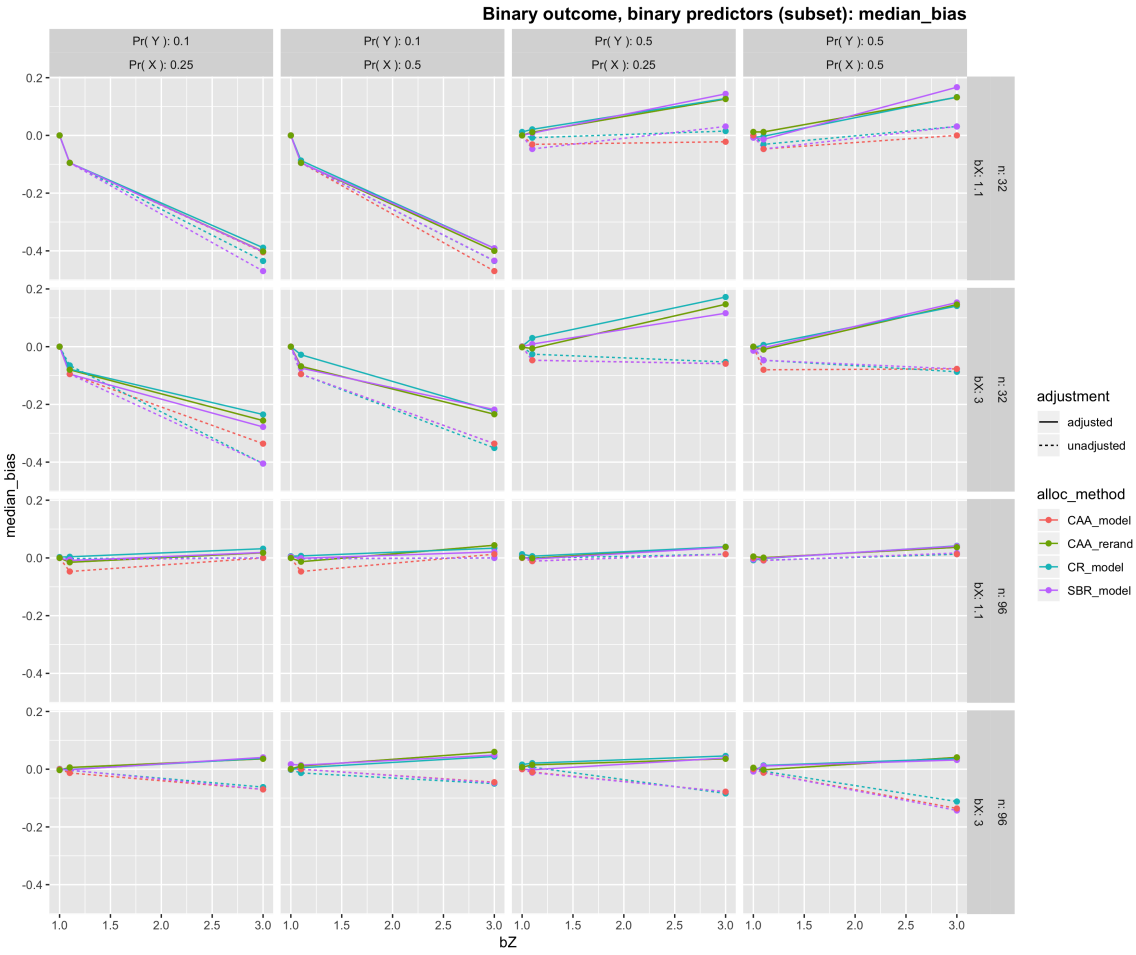

Figure 6.4: Batch 1 subset: Median bias

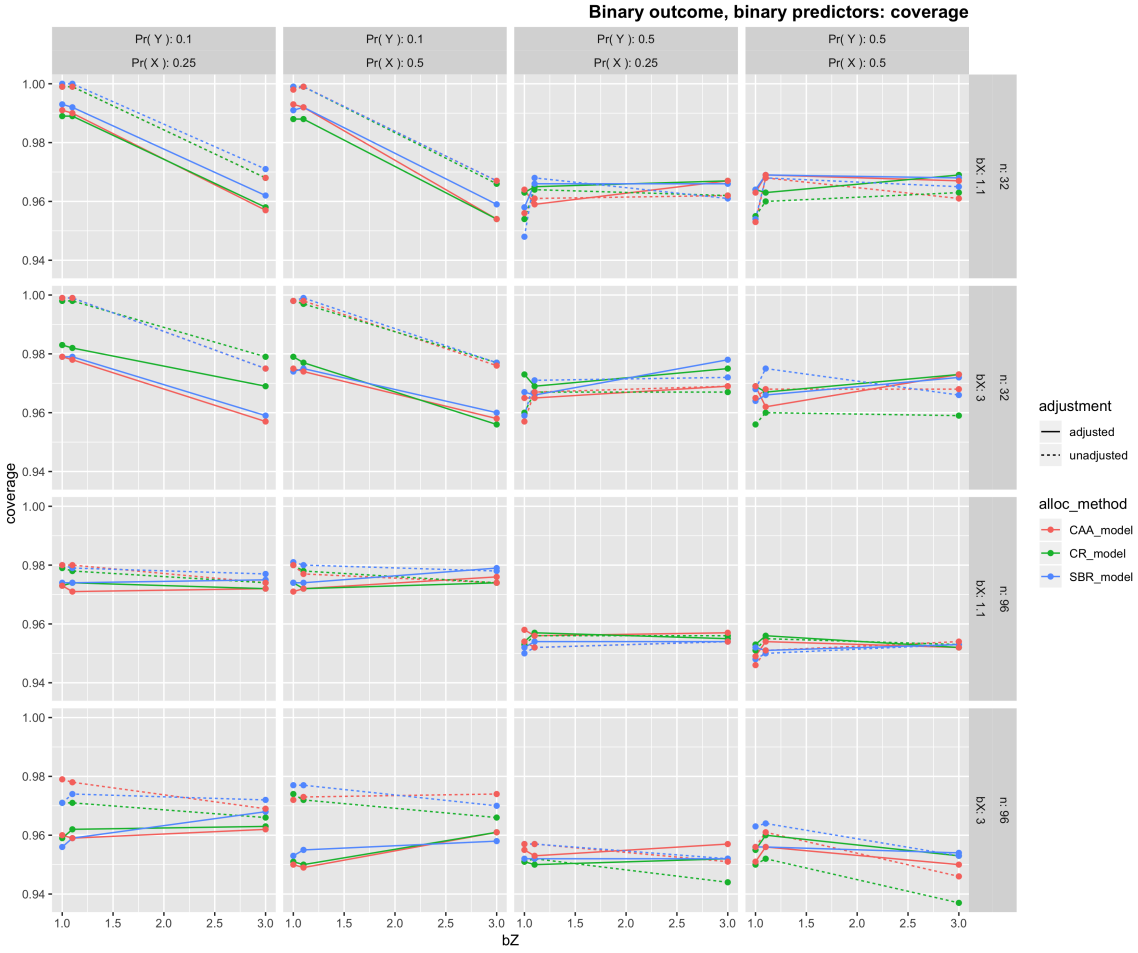

Figure 6.5: Batch 1: Coverage probability

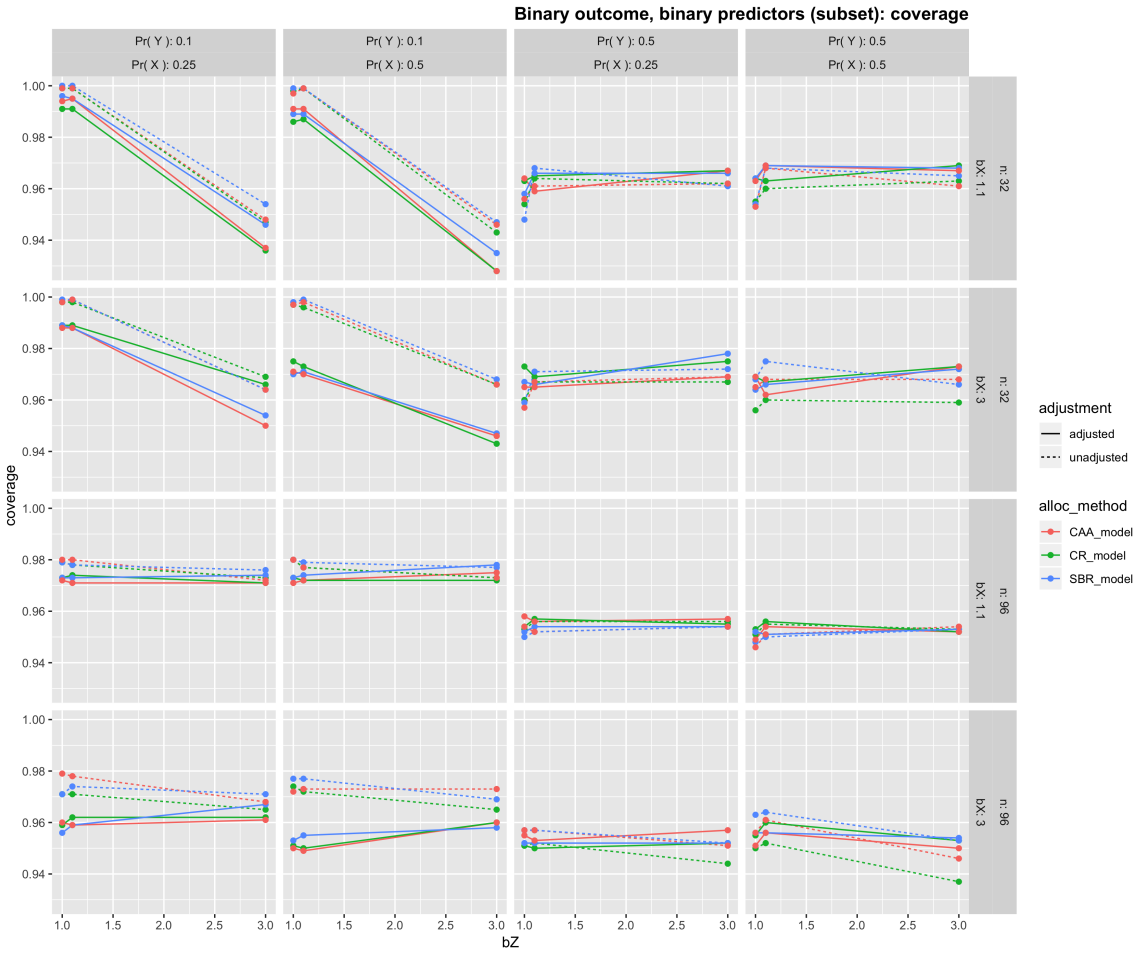

Figure 6.6: Batch 1 subset: Coverage probability

6.2 Batch 2: Binary Outcome, Continuous Predictors

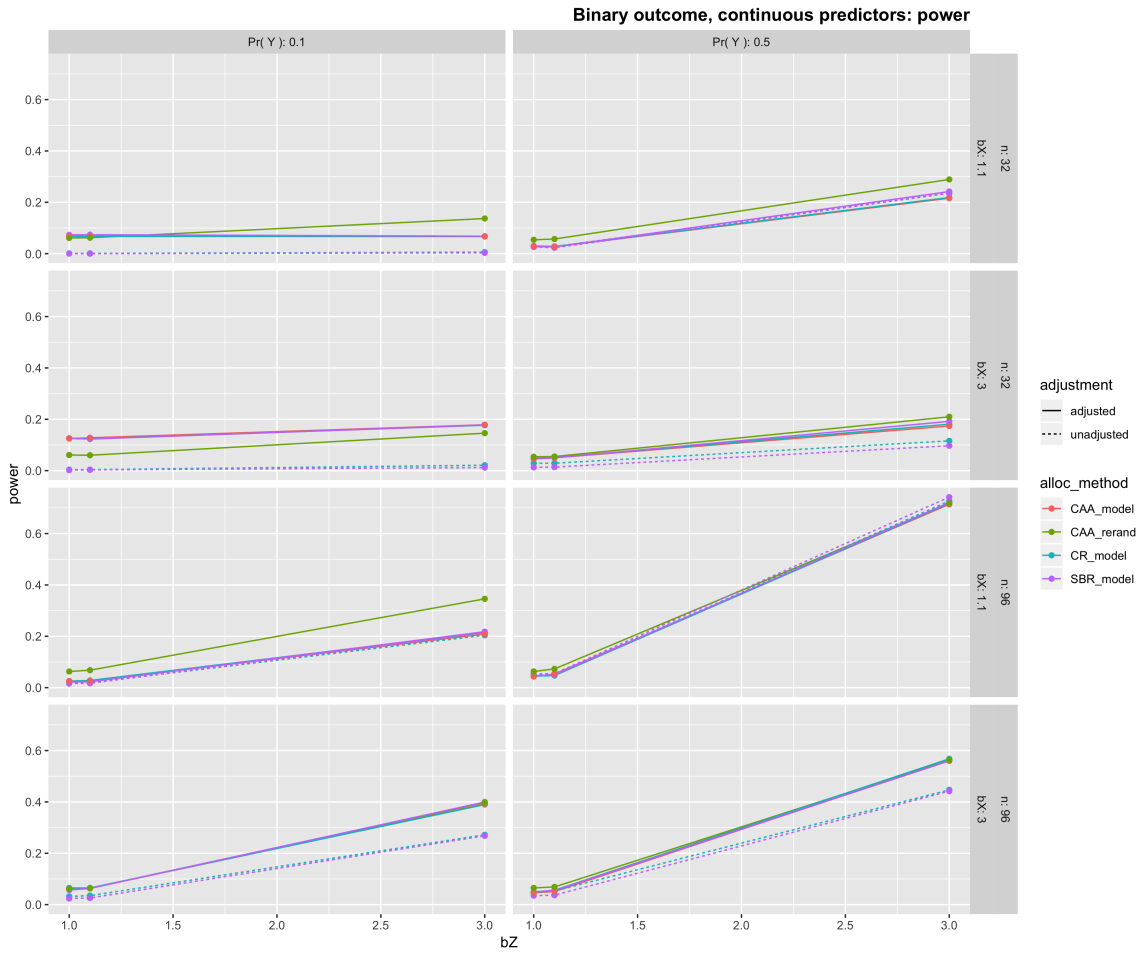

Figure 6.7: Batch 2: Power

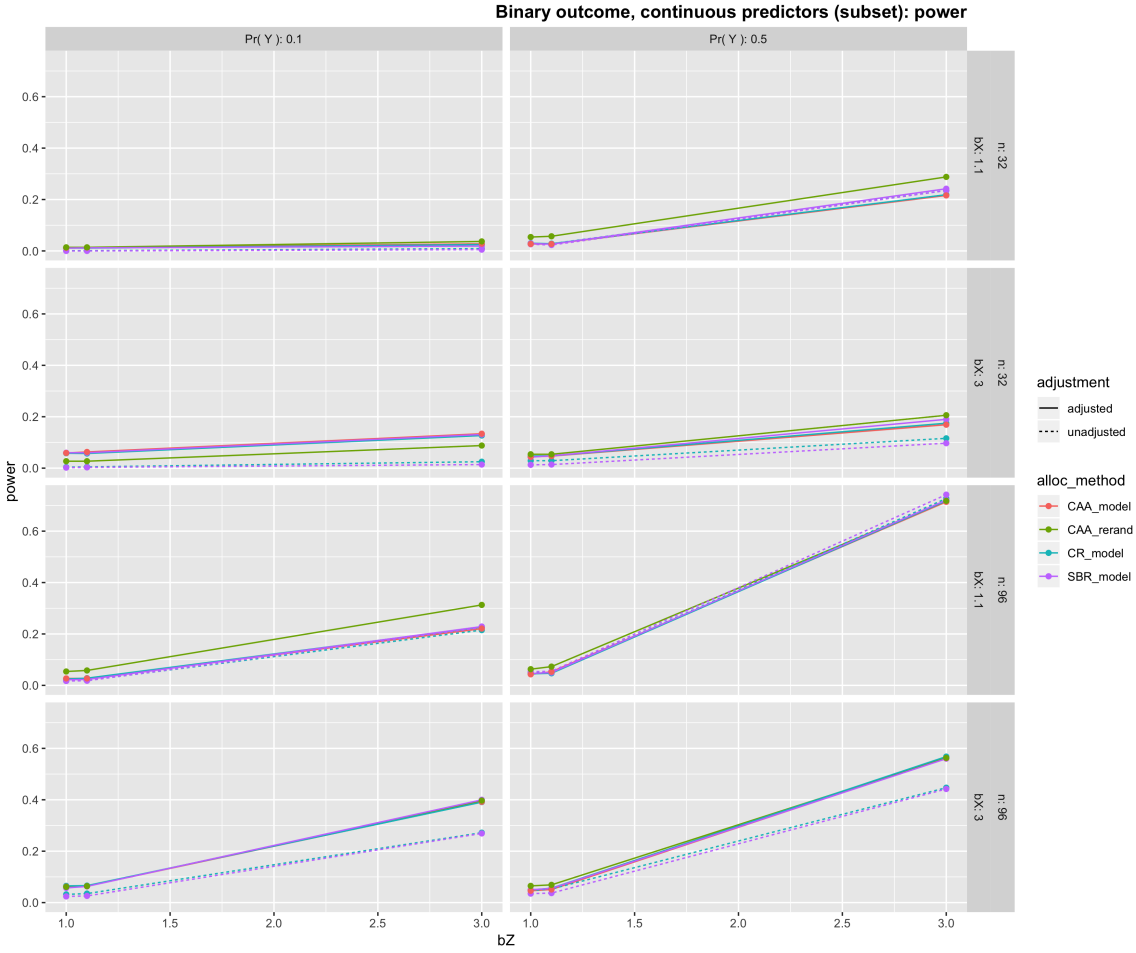

Figure 6.8: Batch 2 subset: Power

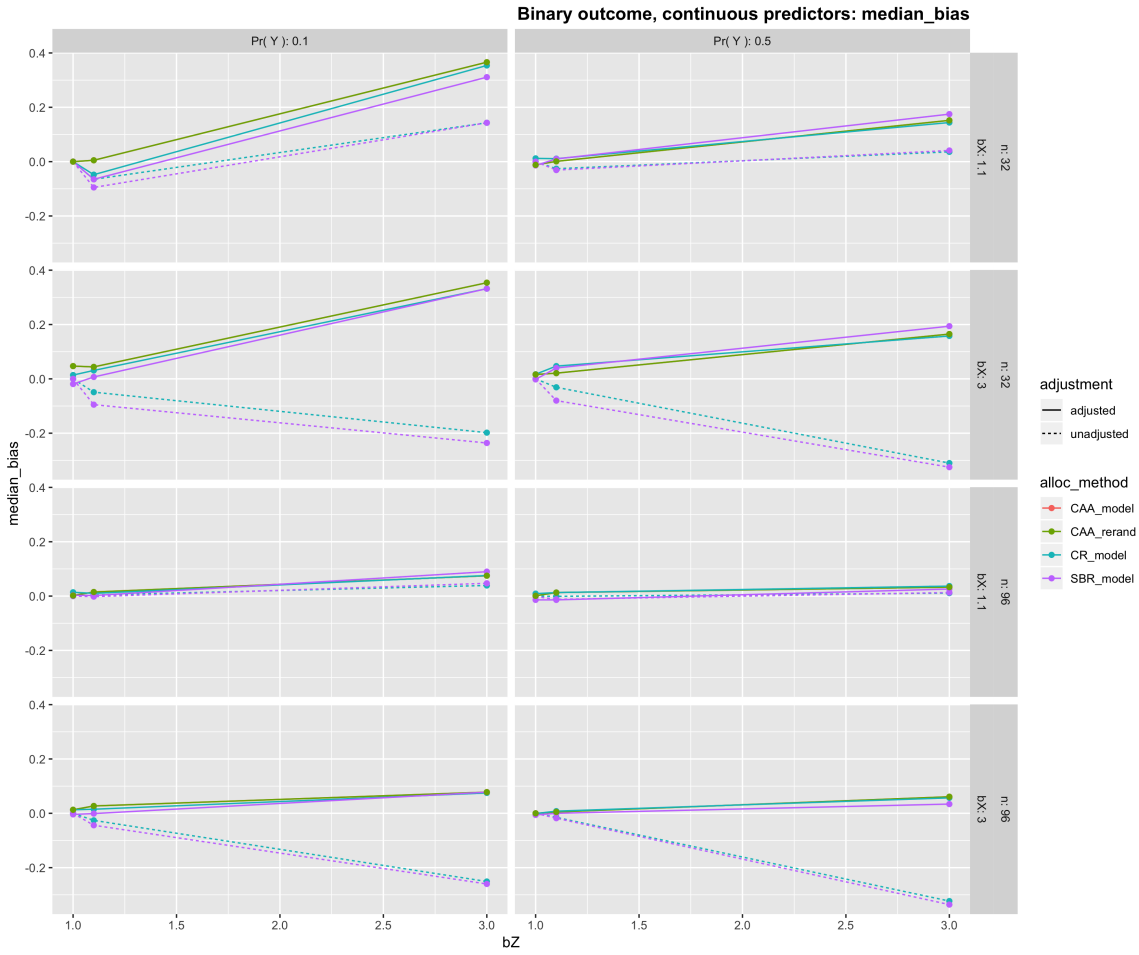

Figure 6.9: Batch 2: Median bias

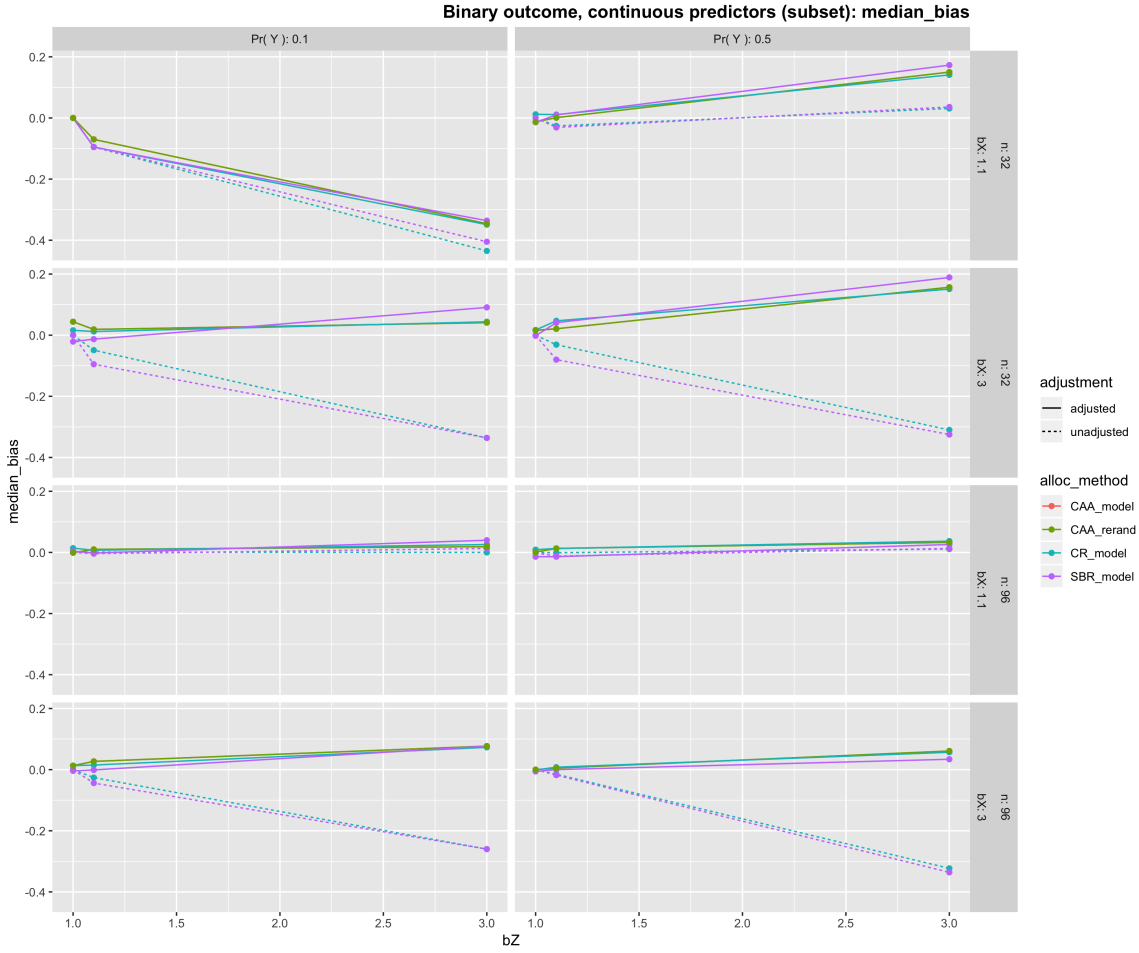

Figure 6.10: Batch 2 subset: Median bias

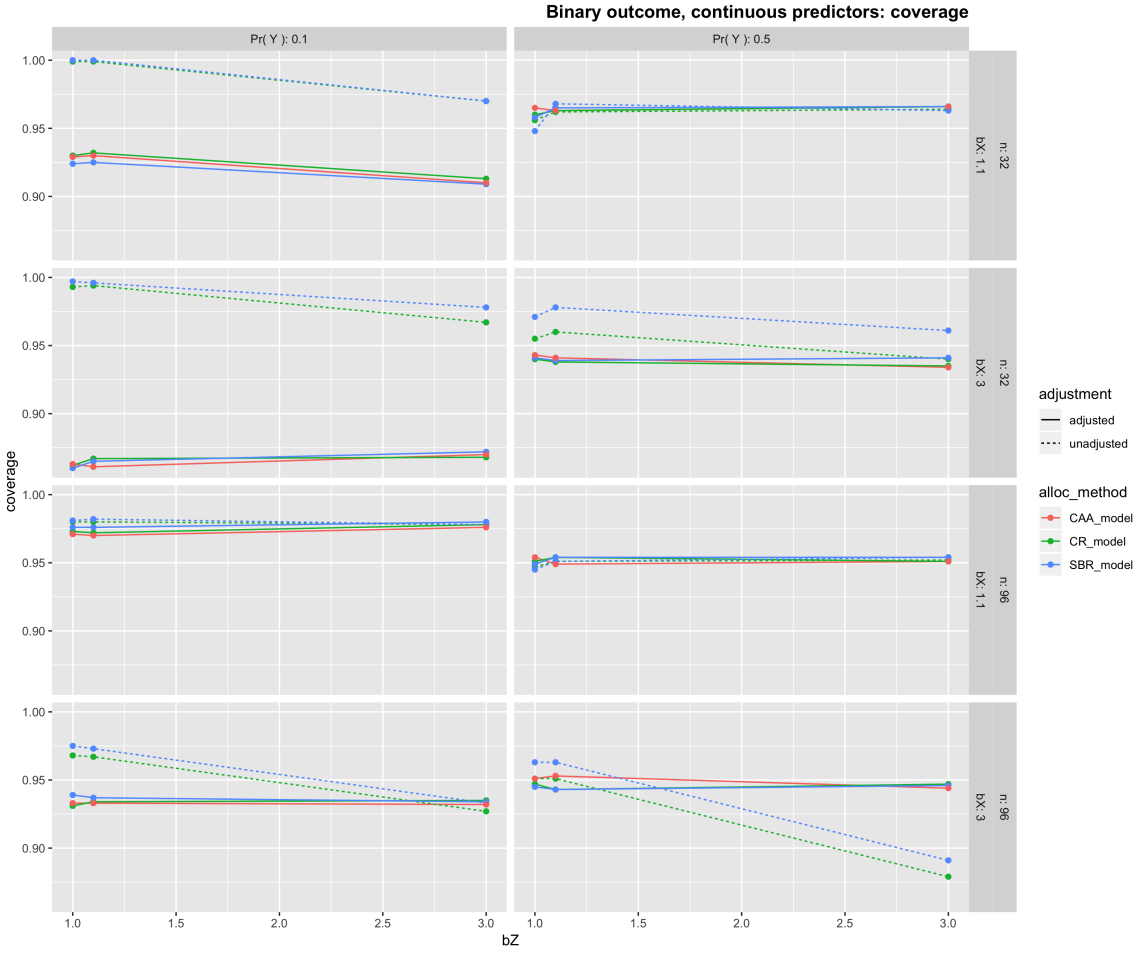

Figure 6.11: Batch 2: Coverage probability

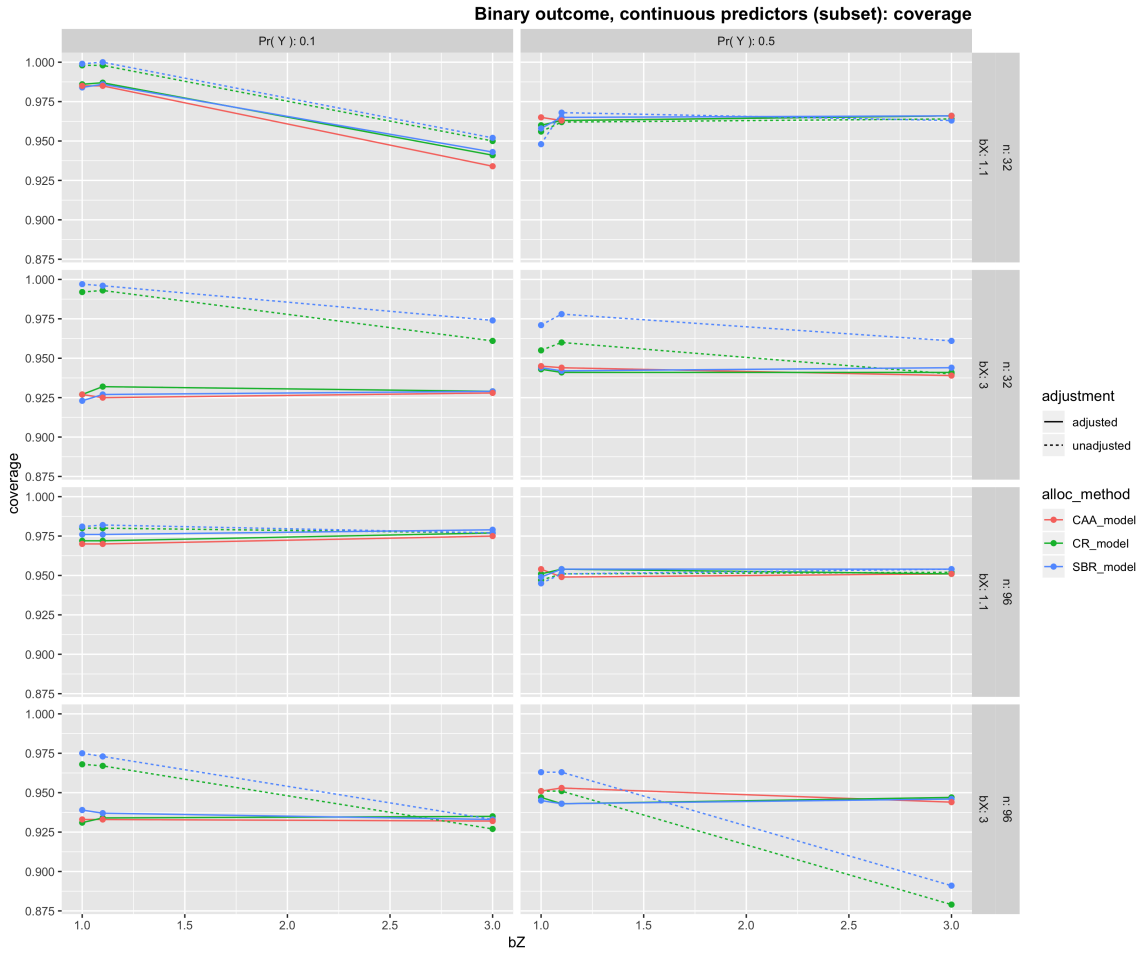

Figure 6.12: Batch 2 subset: Coverage probability

6.3 Batch 3: Continuous Outcome, Binary Predictors

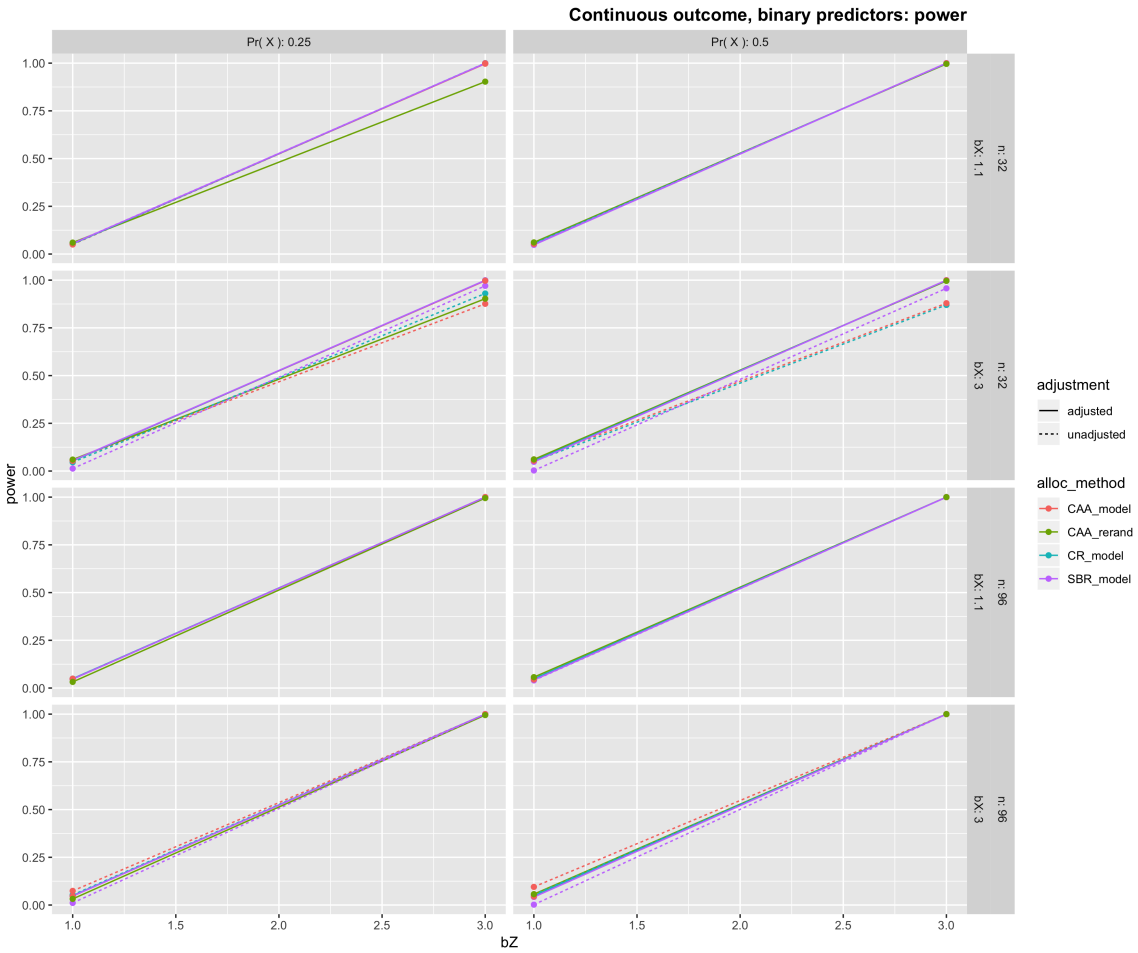

Figure 6.13: Batch 3: Power

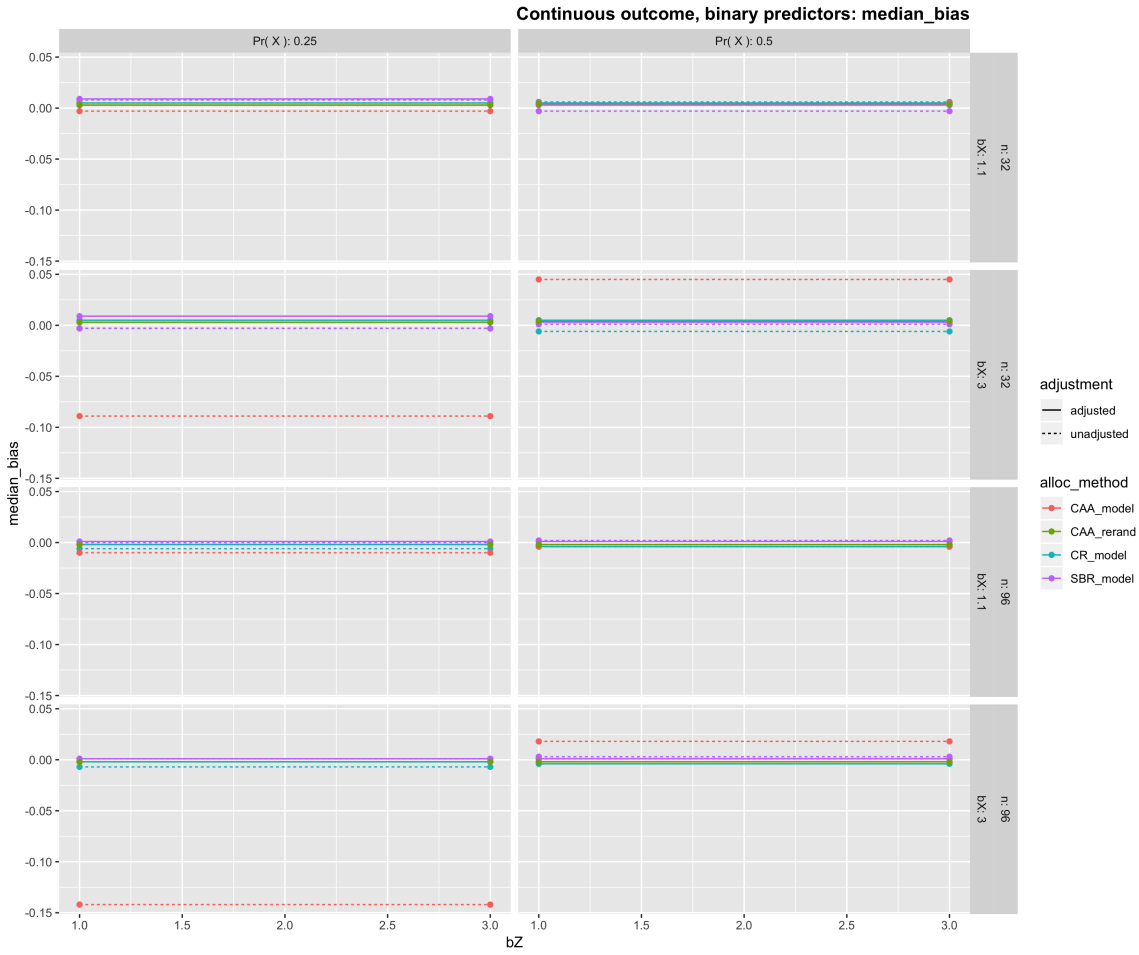

Figure 6.14: Batch 3: Median bias

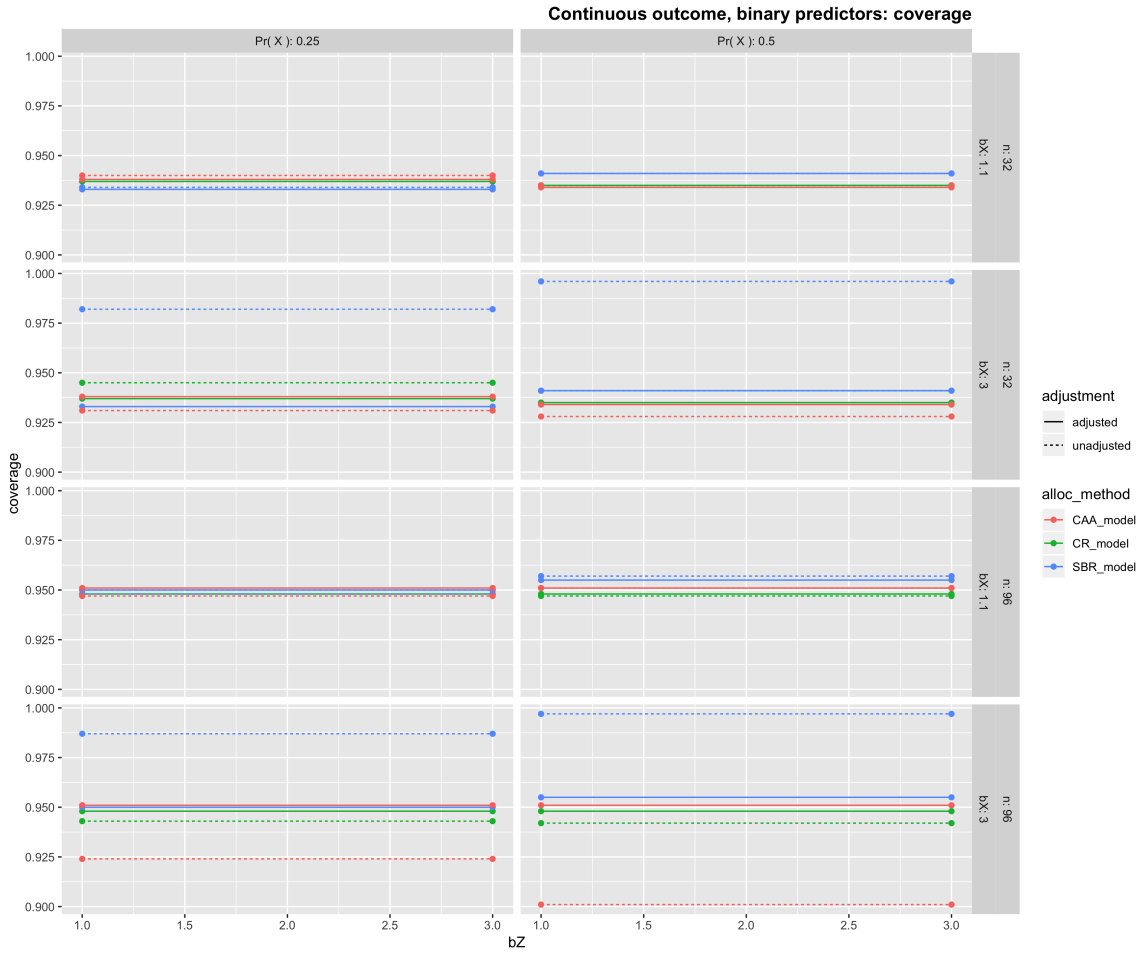

Figure 6.15: Batch 3: Coverage probability

6.4 Batch 4: Continuous Outcome, Continuous Predictors

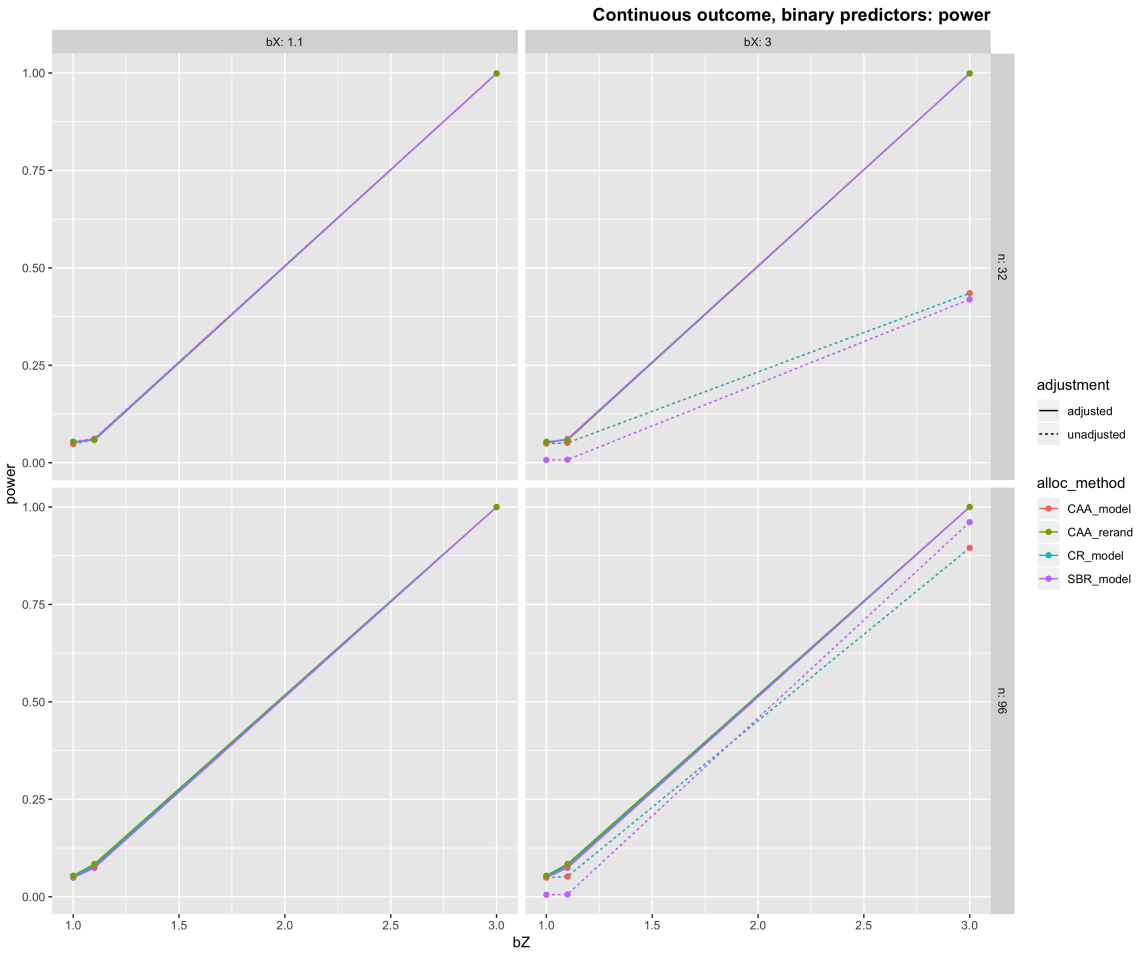

Figure 6.16: Batch 4: Power

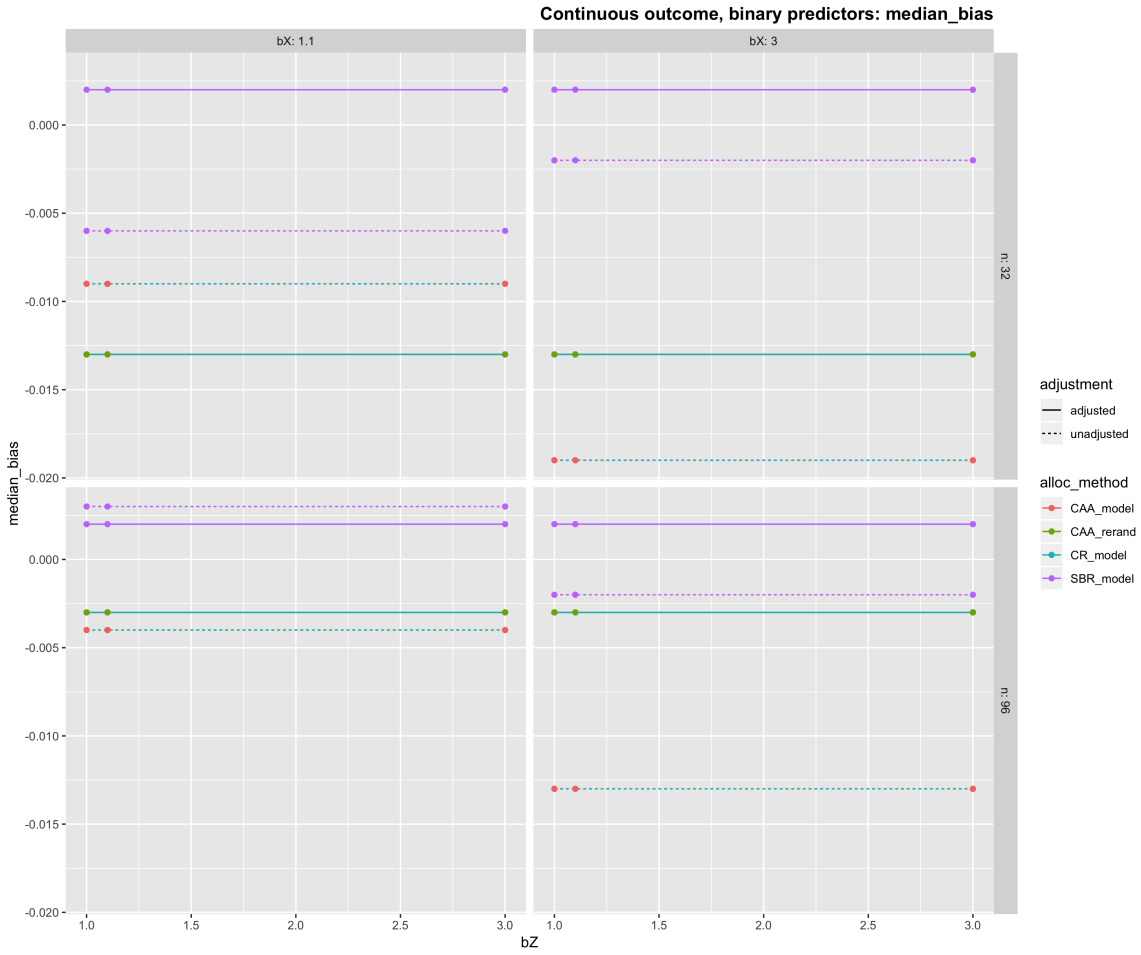

Figure 6.17: Batch 4: Median bias

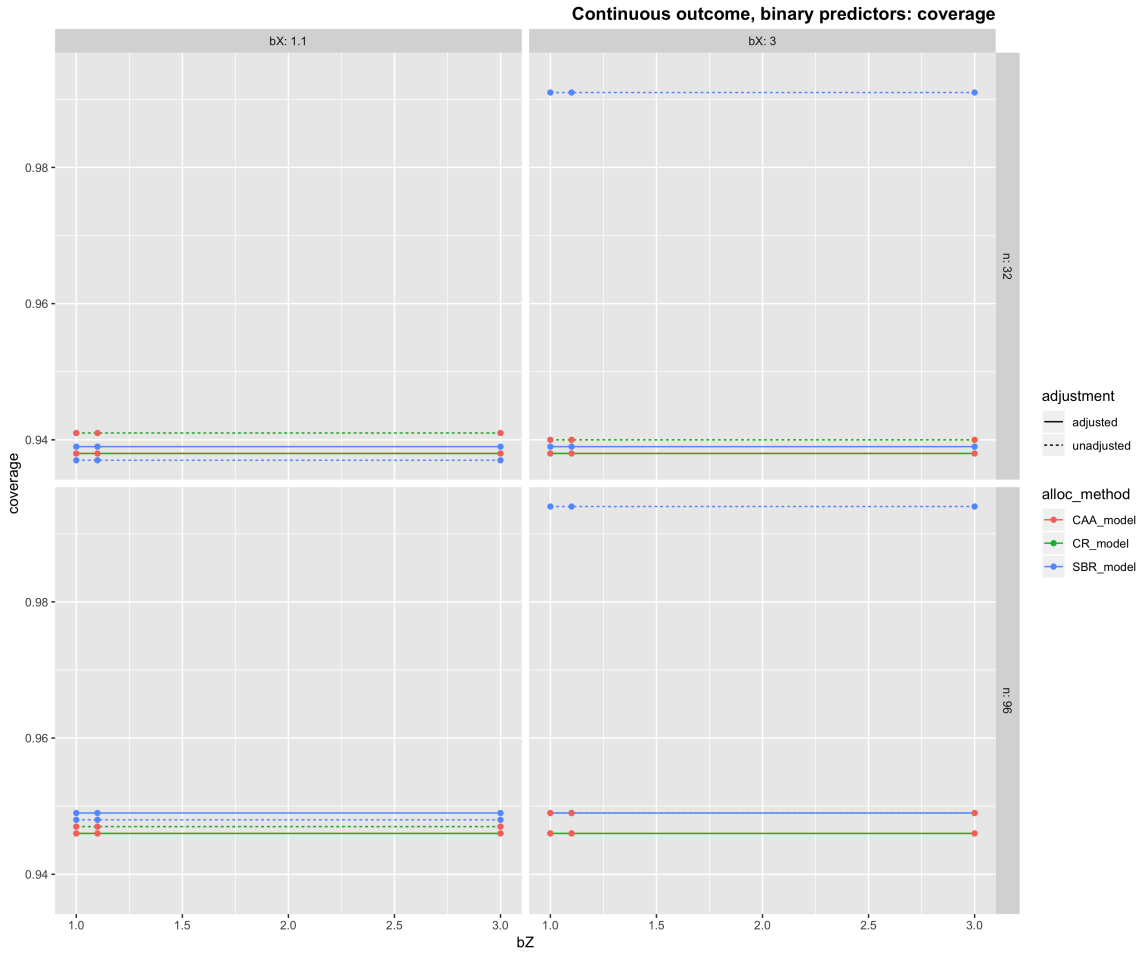

Figure 6.18: Batch 4: Coverage probability

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