Assessing Heterogeneity of Treatment Effects in Observational Studies

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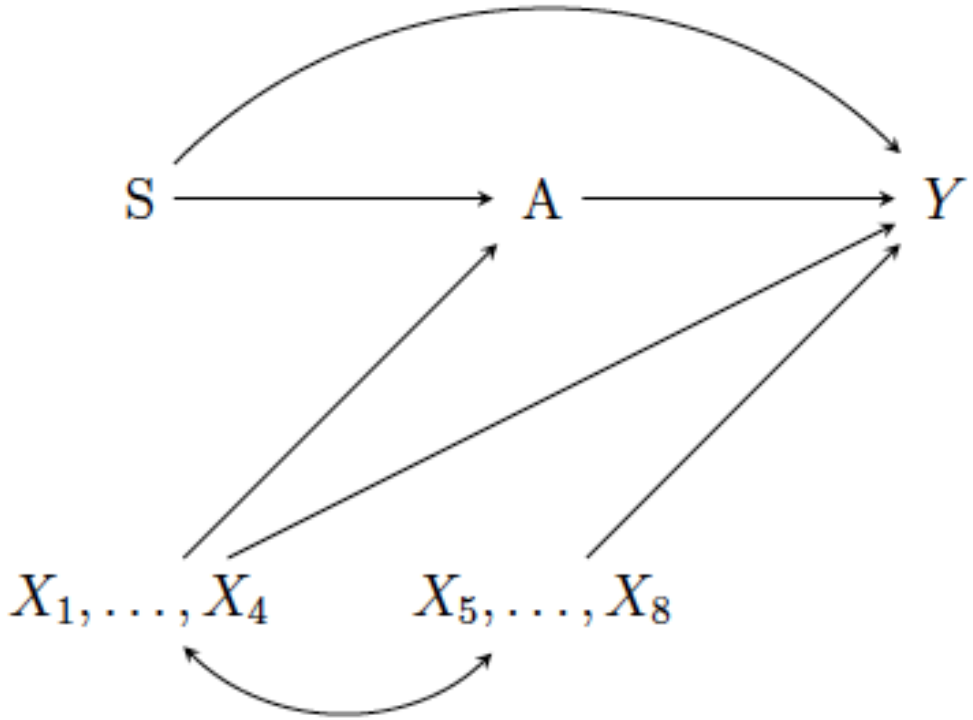
DR Bikal

Clinical Epidemiology, CEB

Introduction

- Observational studies are useful for estimating subgroup-specific average treatment effects
- Large sample sizes give more precise effect estimates
- Require statistical methods to control confounders
  - Outcome model (OM)
  - Inverse probability weighting
  - Doubly robust
  - Matching methods
- large sample behaviour is well understood, however, performance with the finite sample is less studied
- A simulation study was conducted to compare the performance of different estimators for continuous and binary outcomes

Structural model



- S- sub-group indicator
- Xi,j- additional basline coviaraites
- A- treatment variable
- Y – observed outcomes
- Xi,j=1…4- confounding variables affect A and Y
- Xi,j=5…8- outcome predictors affects only Y
- Double-headed arrow shows correlation between different baseline covariates

Simulation study

- Compare the finite sample behaviour of OM, IPW, doubly robust and matching
- Observational studies with no unmeasured confounding and correctly specified parametric models
- Examined both continuous and binary outcomes
- Different scenarios – variable sample size, subgroup prevalence, the magnitude of treatment effects, the correlation between baseline covariates

Targets of inference and measures of performance

- Generated data, applied the estimator and used 100000 replications to assess the performance
- Bias and standard deviation estimated when using each of the estimators
- Multiplied by √n to identify the behaviour of different estimators as n increases

Data generation for S,X, and A

- Subgroup indicator “S” was both considered balance (equal prevalence = 0.5) and imbalance (unequal prevalence = 0.25)
- Other baseline covariates “X” from an independent standard normal distribution
- Case scenario where baseline covariates in “X” correlated with each other varying between -0.2 and 0.2
- Treatment choice in each subgroup using a binary indicator “A” but all other coefficients of baseline covariates were the same

Data generation for continuous “Y”

- Examined 4 different average treatment effects (ATE) for S=1 namely, ATE(S=1) = 0, -0.5,-1, or -2.
- Each of the treatment effects, 4 different versions of effect modification:
  - ATE(S=0) = ATE(S=1) (absence of effect modification);
  - ATE (S=0) = -0.5 + ATE(S=1);
  - ATE(S=0) =-1 + ATE(S=1); and
  - ATE (S=0) = - ATE(S=1)

Model specification in the simulation study

- Used correctly specified parametric models
- For the probability of treatment
  - Logistic regression model (considered all pretreatment covariates, including confounding variables and pure outcome indicators, X1,…., X8 and S, and product term X1 × S)
  - Logistic regression model – included only confounding variables, X1,…,X4 and S, and product term X1 × S
- For continuous outcome – linear regression model with effects for X1,…, X8 and S, the product term X1 × S, treatment A, and the product term A × S
- All simulations were carried out in Stata version MP/15.1

Simulation Results

Parameters for continuous outcomes

Web Table 1: Parameter values for the simulation study for continuous outcomes.

$\lambda_{1,1}$	$\lambda_{0,1}$	$ATE(S=1)$	$\lambda_{1,0}$	$\lambda_{0,0}$	$ATE(S=0)$	$dATE$
0	0	0	0	0	0	0
0	0	0	-0.5	0	-0.5	0.5
0	0	0	-1	0	-1	1
0	0	0	0	0	0	0
-0.5	0	-0.5	-0.5	0	-0.5	0
-0.5	0	-0.5	-1	0	-1	0.5
-0.5	0	-0.5	-1.5	0	-1.5	1
-0.5	0	-0.5	0.5	0	0.5	-1
-1	0	-1	-1	0	-1	0
-1	0	-1	-1.5	0	-1.5	0.5
-1	0	-1	-2	0	-2	1
-1	0	-1	1	0	1	-2
-2	0	-2	-2	0	-2	0
-2	0	-2	-2.5	0	-2.5	0.5
-2	0	-2	-3	0	-3	1
-2	0	-2	2	0	2	-4

$\lambda_{a,s}$ is the subgroup-specific mean; $ATE(S=s)$ is the mean difference of stratum s, so $ATE(S=s) = \lambda_{1,s} - \lambda_{0,s}$; $dATE = ATE(S=1) - ATE(S=0)$.

Simulation results for continuous outcomes

- Bias and standard deviation in OM and DR was low as compared to IPW and MT however when the sample size increases it start to decrease

Correlated baseline covariates when $\Pr[S=1|X]=0.5$

Web Table 3: Bias multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	$ATE(S=1)$	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	0.005	-0.158	-1.919	0.032	0.004	-0.006	-0.887
500	0.0	-0.5	0.5	-0.000	-0.044	-1.848	0.020	0.014	0.010	-0.904
500	0.0	-1.0	1.0	-0.004	-0.362	-1.859	-0.026	-0.014	0.008	-0.819
500	0.0	0.0	0.0	0.015	-0.028	-1.795	0.029	0.027	0.019	-0.957
500	-0.5	-0.5	0.0	0.009	0.100	-1.651	0.004	0.004	-0.000	-0.780
500	-0.5	-1.0	0.5	-0.013	-0.227	-1.823	-0.020	-0.006	-0.004	-0.907
500	-0.5	-1.5	1.0	0.017	0.202	-1.575	0.031	0.024	0.017	-0.859
500	-0.5	0.5	-1.0	-0.031	0.047	-1.834	-0.044	-0.041	-0.032	-0.984
500	-1.0	-1.0	0.0	-0.005	-0.178	-1.919	0.032	0.004	-0.006	-0.887
500	-1.0	-1.5	0.5	-0.000	-0.067	-1.848	0.020	0.014	0.010	-0.904
500	-1.0	-2.0	1.0	-0.004	-0.403	-1.859	-0.026	-0.014	-0.008	-0.819
500	-1.0	1.0	-2.0	0.015	0.010	-1.795	0.029	0.027	0.019	-0.957
500	-2.0	-2.0	0.0	0.009	0.096	-1.651	0.004	0.004	0.000	-0.780
500	-2.0	-2.5	0.5	-0.013	-0.260	-1.823	-0.020	-0.006	-0.004	-0.907
500	-2.0	-3.0	1.0	0.017	0.224	-1.575	0.031	0.024	0.017	-0.859
500	-2.0	2.0	-4.0	-0.031	0.103	-1.834	-0.044	-0.041	-0.032	-0.984
1000	0.0	0.0	0.0	0.000	-0.175	-1.770	0.005	0.002	0.002	-1.015
1000	0.0	-0.5	0.5	0.013	-0.124	-1.775	0.042	0.033	0.030	-1.045
1000	0.0	-1.0	1.0	-0.001	-0.104	-1.638	-0.035	-0.025	-0.021	-1.023
1000	0.0	0.0	0.0	0.004	-0.074	-1.653	-0.031	-0.010	-0.001	-1.000
1000	-0.5	-0.5	0.0	0.036	-0.090	-1.708	0.019	0.018	0.017	-1.002
1000	-0.5	-1.0	0.5	-0.008	-0.150	-1.748	-0.052	-0.024	-0.008	-0.890
1000	-0.5	-1.5	1.0	-0.006	-0.207	-1.878	0.003	-0.005	-0.009	-1.085
1000	-0.5	0.5	-1.0	-0.002	-0.009	-1.665	0.011	0.011	0.009	-0.978
1000	-1.0	-1.0	0.0	0.000	-0.210	-1.770	0.005	0.002	0.002	-1.015
1000	-1.0	-1.5	0.5	0.013	-0.138	-1.775	0.042	0.033	0.030	-1.045
1000	-1.0	-2.0	1.0	-0.001	-0.107	-1.638	-0.035	-0.025	-0.021	-1.023
1000	-1.0	1.0	-2.0	0.004	-0.052	-1.653	-0.031	-0.010	-0.001	-1.000
1000	-2.0	-2.0	0.0	0.036	-0.105	-1.708	0.019	0.018	0.017	-1.002
1000	-2.0	-2.5	0.5	-0.008	-0.177	-1.748	-0.052	-0.024	-0.008	-0.890
1000	-2.0	-3.0	1.0	-0.006	-0.247	-1.878	0.003	-0.005	-0.009	-1.085
1000	-2.0	2.0	-4.0	-0.002	0.033	-1.665	0.011	0.011	0.009	-0.978
5000	0.0	0.0	0.0	0.023	0.187	-1.000	0.007	0.013	0.013	-1.115
5000	0.0	-0.5	0.5	-0.015	-0.060	-1.198	-0.056	-0.055	-0.055	-1.301
5000	0.0	-1.0	1.0	0.008	0.292	-0.934	0.030	0.026	0.021	-1.100
5000	0.0	0.0	0.0	0.002	0.373	-0.846	-0.007	-0.002	-0.005	-1.176
5000	-0.5	-0.5	0.0	0.015	-0.083	-1.211	0.055	0.056	0.056	-1.207
5000	-0.5	-1.0	0.5	0.026	0.080	-1.046	0.033	0.034	0.035	-1.213
5000	-0.5	-1.5	1.0	-0.001	0.064	-1.088	-0.011	-0.008	-0.007	-1.132
5000	-0.5	0.5	-1.0	0.003	0.073	-1.207	-0.031	-0.025	-0.020	-1.333
5000	-1.0	-1.0	0.0	0.023	0.183	-1.000	0.007	0.013	0.013	-1.115
5000	-1.0	-1.5	0.5	-0.015	-0.060	-1.198	-0.056	-0.055	-0.055	-1.301
5000	-1.0	-2.0	1.0	0.008	0.292	-0.934	0.030	0.026	0.021	-1.100
5000	-1.0	1.0	-2.0	0.002	0.382	-0.846	-0.007	-0.002	-0.005	-1.176
5000	-2.0	-2.0	0.0	0.015	-0.091	-1.211	0.055	0.056	0.056	-1.207
5000	-2.0	-2.5	0.5	0.026	0.101	-1.046	0.033	0.034	0.035	-1.213
5000	-2.0	-3.0	1.0	-0.001	0.056	-1.088	-0.011	-0.008	-0.007	-1.132
5000	-2.0	2.0	-4.0	0.003	0.070	-1.207	-0.031	-0.025	-0.020	-1.333

Web Table 4: Standard deviation multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	$ATE(S=1)$	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	4.293	65.082	34.936	9.002	6.845	6.098	19.082
500	0.0	-0.5	0.5	4.310	69.719	34.653	9.037	6.860	6.128	19.139
500	0.0	-1.0	1.0	4.318	57.310	34.720	8.601	6.866	6.128	19.284
500	0.0	0.0	0.0	4.310	56.995	34.679	8.913	6.842	6.106	19.276
500	-0.5	-0.5	0.0	4.301	60.684	34.619	8.560	6.844	6.112	19.207
500	-0.5	-1.0	0.5	4.303	61.682	34.717	8.597	6.858	6.126	19.227
500	-0.5	-1.5	1.0	4.311	62.521	34.833	8.818	6.862	6.129	19.169
500	-0.5	0.5	-1.0	4.313	60.770	34.453	8.800	6.857	6.136	19.209
500	-1.0	-1.0	0.0	4.293	68.675	34.936	9.002	6.845	6.098	19.082
500	-1.0	-1.5	0.5	4.310	72.687	34.653	9.037	6.860	6.128	19.139
500	-1.0	-2.0	1.0	4.318	61.043	34.720	8.601	6.866	6.128	19.284
500	-1.0	1.0	-2.0	4.310	55.879	34.679	8.913	6.842	6.106	19.276
500	-2.0	-2.0	0.0	4.301	66.941	34.619	8.560	6.844	6.112	19.207
500	-2.0	-2.5	0.5	4.303	66.772	34.717	8.597	6.858	6.126	19.227
500	-2.0	-3.0	1.0	4.311	68.604	34.833	8.818	6.862	6.129	19.169
500	-2.0	2.0	-4.0	4.313	58.088	34.453	8.800	6.857	6.136	19.209
1000	0.0	0.0	0.0	4.284	53.797	38.096	8.587	7.139	6.434	19.639
1000	0.0	-0.5	0.5	4.273	54.578	38.433	8.348	7.147	6.408	19.669
1000	0.0	-1.0	1.0	4.271	53.107	37.860	8.281	7.106	6.399	19.669
1000	0.0	0.0	0.0	4.279	52.337	37.858	8.573	7.137	6.416	19.734
1000	-0.5	-0.5	0.0	4.275	58.404	38.090	8.510	7.153	6.419	19.692
1000	-0.5	-1.0	0.5	4.288	54.868	37.996	8.280	7.152	6.436	19.685
1000	-0.5	-1.5	1.0	4.258	58.756	38.113	8.460	7.113	6.387	19.713
1000	-0.5	0.5	-1.0	4.271	51.725	37.988	8.380	7.156	6.425	19.683
1000	-1.0	-1.0	0.0	4.284	57.023	38.096	8.587	7.139	6.434	19.639
1000	-1.0	-1.5	0.5	4.273	58.072	38.433	8.348	7.147	6.408	19.669
1000	-1.0	-2.0	1.0	4.271	56.418	37.860	8.281	7.106	6.399	19.669
1000	-1.0	1.0	-2.0	4.279	51.646	37.858	8.573	7.137	6.416	19.734
1000	-2.0	-2.0	0.0	4.275	63.542	38.090	8.510	7.153	6.419	19.692
1000	-2.0	-2.5	0.5	4.288	60.071	37.996	8.280	7.152	6.436	19.685
1000	-2.0	-3.0	1.0	4.258	64.154	38.113	8.460	7.113	6.387	19.713
1000	-2.0	2.0	-4.0	4.271	50.757	37.988	8.380	7.156	6.425	19.683
5000	0.0	0.0	0.0	4.258	51.604	44.757	8.093	7.640	7.074	21.013
5000	0.0	-0.5	0.5	4.255	52.400	44.692	8.200	7.658	7.070	21.091
5000	0.0	-1.0	1.0	4.272	56.201	45.191	8.209	7.668	7.075	20.974
5000	0.0	0.0	0.0	4.261	55.878	44.743	8.221	7.610	7.069	20.992
5000	-0.5	-0.5	0.0	4.270	53.269	44.776	8.039	7.607	7.069	21.032
5000	-0.5	-1.0	0.5	4.247	53.511	44.611	8.061	7.602	7.047	20.993
5000	-0.5	-1.5	1.0	4.259	54.813	44.634	8.049	7.624	7.076	21.004
5000	-0.5	0.5	-1.0	4.259	54.291	45.090	8.186	7.655	7.075	21.068
5000	-1.0	-1.0	0.0	4.258	54.576	44.757	8.093	7.640	7.074	21.013
5000	-1.0	-1.5	0.5	4.255	55.643	44.692	8.200	7.658	7.070	21.091
5000	-1.0	-2.0	1.0	4.272	59.554	45.191	8.209	7.668	7.075	20.974
5000	-1.0	1.0	-2.0	4.261	55.049	44.743	8.221	7.610	7.069	20.992
5000	-2.0	-2.0	0.0	4.270	58.372	44.776	8.039	7.607	7.069	21.032
5000	-2.0	-2.5	0.5	4.247	58.404	44.611	8.061	7.602	7.047	20.993
5000	-2.0	-3.0	1.0	4.259	59.817	44.634	8.049	7.624	7.076	21.004
5000	-2.0	2.0	-4.0	4.259	52.565	45.090	8.186	7.655	7.075	21.068

Simulation results for continuous outcome

Independent baseline covariates when $\Pr[S = 1|X] = 0.25$

Web Table 5: Bias multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	$ATE(S=1)$	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	-0.007	1.166	3.223	-0.024	-0.015	-0.013	2.232
500	0.0	-0.5	0.5	0.003	1.622	3.477	0.036	0.030	0.024	2.422
500	0.0	-1.0	1.0	0.017	1.171	3.279	0.035	0.027	0.027	2.463
500	0.0	0.0	0.0	-0.007	1.411	3.364	-0.007	-0.012	-0.019	2.481
500	-0.5	-0.5	0.0	0.002	1.079	3.295	-0.004	-0.000	-0.004	2.432
500	-0.5	-1.0	0.5	-0.019	1.129	3.310	-0.082	-0.055	-0.050	2.532
500	-0.5	-1.5	1.0	0.002	1.275	3.292	-0.012	-0.014	-0.008	2.480
500	-0.5	0.5	-1.0	-0.005	1.483	3.415	0.015	0.008	0.007	2.490
500	-1.0	-1.0	0.0	-0.007	1.307	3.223	-0.024	-0.015	-0.013	2.232
500	-1.0	-1.5	0.5	0.003	1.774	3.477	0.036	0.030	0.024	2.422
500	-1.0	-2.0	1.0	0.017	1.290	3.279	0.035	0.027	0.027	2.463
500	-1.0	1.0	-2.0	-0.007	1.470	3.364	-0.007	-0.012	-0.019	2.481
500	-2.0	-2.0	0.0	0.002	1.269	3.295	-0.004	-0.000	-0.004	2.432
500	-2.0	-2.5	0.5	-0.019	1.312	3.310	-0.082	-0.055	-0.050	2.532
500	-2.0	-3.0	1.0	0.002	1.454	3.292	-0.012	-0.014	-0.008	2.480
500	-2.0	2.0	-4.0	-0.005	1.574	3.415	0.015	0.008	0.007	2.490
1000	0.0	0.0	0.0	0.019	1.023	2.535	0.049	0.045	0.043	1.983
1000	0.0	-0.5	0.5	0.001	0.729	2.345	0.021	0.018	0.016	2.034
1000	0.0	-1.0	1.0	-0.026	0.630	2.234	0.002	-0.016	-0.025	2.059
1000	0.0	0.0	0.0	-0.011	0.842	2.458	0.014	-0.001	-0.006	2.047
1000	-0.5	-0.5	0.0	0.027	0.891	2.480	0.045	0.039	0.038	2.043
1000	-0.5	-1.0	0.5	0.002	1.213	2.692	0.019	0.026	0.020	2.127
1000	-0.5	-1.5	1.0	-0.010	0.986	2.532	0.025	0.026	0.025	2.148
1000	-0.5	0.5	-1.0	-0.022	1.066	2.569	-0.023	-0.018	-0.015	2.156
1000	-1.0	-1.0	0.0	0.019	1.128	2.535	0.049	0.045	0.043	1.983
1000	-1.0	-1.5	0.5	0.001	0.797	2.345	0.021	0.018	0.016	2.034
1000	-1.0	-2.0	1.0	-0.026	0.698	2.234	0.002	-0.016	-0.025	2.059
1000	-1.0	1.0	-2.0	-0.011	0.899	2.458	0.014	-0.001	-0.006	2.047
1000	-2.0	-2.0	0.0	0.027	1.035	2.480	0.045	0.039	0.038	2.043
1000	-2.0	-2.5	0.5	0.002	1.379	2.692	0.019	0.026	0.020	2.127
1000	-2.0	-3.0	1.0	-0.010	1.119	2.532	0.025	0.026	0.025	2.148
1000	-2.0	2.0	-4.0	-0.022	1.180	2.569	-0.023	-0.018	-0.015	2.156
5000	0.0	0.0	0.0	0.023	0.239	1.076	0.033	0.033	0.029	1.327
5000	0.0	-0.5	0.5	0.015	0.433	1.219	0.036	0.038	0.038	1.508
5000	0.0	-1.0	1.0	0.008	0.250	1.003	0.007	0.006	0.000	1.571
5000	0.0	0.0	0.0	0.023	0.366	1.136	0.038	0.039	0.039	1.505
5000	-0.5	-0.5	0.0	-0.013	0.184	1.030	-0.013	-0.017	-0.021	1.403
5000	-0.5	-1.0	0.5	0.006	0.570	1.299	0.003	0.012	0.014	1.484
5000	-0.5	-1.5	1.0	0.032	0.156	0.965	-0.019	-0.014	-0.011	1.441
5000	-0.5	0.5	-1.0	-0.024	0.420	1.184	-0.015	-0.017	-0.023	1.349
5000	-1.0	-1.0	0.0	0.023	0.265	1.076	0.033	0.033	0.029	1.327
5000	-1.0	-1.5	0.5	0.015	0.479	1.219	0.036	0.038	0.038	1.508
5000	-1.0	-2.0	1.0	0.008	0.285	1.003	0.007	0.006	0.000	1.571
5000	-1.0	1.0	-2.0	0.023	0.386	1.136	0.038	0.039	0.039	1.505
5000	-2.0	-2.0	0.0	-0.013	0.239	1.030	-0.013	-0.017	-0.021	1.403
5000	-2.0	-2.5	0.5	0.006	0.655	1.299	0.003	0.012	0.014	1.484
5000	-2.0	-3.0	1.0	0.032	0.212	0.965	-0.019	-0.014	-0.011	1.441
5000	-2.0	2.0	-4.0	-0.024	0.434	1.184	-0.015	-0.017	-0.023	1.349

Web Table 6: Standard deviation multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	ATE(S=1)	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	4.795	53.787	35.779	9.013	7.352	6.661	22.920
500	0.0	-0.5	0.5	4.798	57.128	35.693	8.972	7.380	6.690	22.837
500	0.0	-1.0	1.0	4.798	59.536	36.000	9.725	7.368	6.662	22.989
500	0.0	0.0	0.0	4.813	56.226	36.205	8.957	7.401	6.697	22.987
500	-0.5	-0.5	0.0	4.813	58.907	35.999	8.949	7.371	6.690	22.946
500	-0.5	-1.0	0.5	4.813	58.289	35.869	8.770	7.388	6.711	22.976
500	-0.5	-1.5	1.0	4.810	62.982	35.930	9.146	7.355	6.676	22.938
500	-0.5	0.5	-1.0	4.787	57.881	35.969	8.881	7.353	6.668	22.899
500	-1.0	-1.0	0.0	4.795	57.169	35.779	9.013	7.352	6.661	22.920
500	-1.0	-1.5	0.5	4.798	60.550	35.693	8.972	7.380	6.690	22.837
500	-1.0	-2.0	1.0	4.798	63.185	36.000	9.725	7.368	6.662	22.989
500	-1.0	1.0	-2.0	4.813	57.195	36.205	8.957	7.401	6.697	22.987
500	-2.0	-2.0	0.0	4.813	64.294	35.999	8.949	7.371	6.690	22.946
500	-2.0	-2.5	0.5	4.813	63.893	35.869	8.770	7.388	6.711	22.976
500	-2.0	-3.0	1.0	4.810	69.368	35.930	9.146	7.355	6.676	22.938
500	-2.0	2.0	-4.0	4.787	59.964	35.969	8.881	7.353	6.668	22.899
1000	0.0	0.0	0.0	4.763	53.143	39.106	8.595	7.621	6.977	23.723
1000	0.0	-0.5	0.5	4.742	52.963	39.332	8.583	7.604	6.956	23.720
1000	0.0	-1.0	1.0	4.763	55.256	39.281	8.807	7.623	6.970	23.598
1000	0.0	0.0	0.0	4.770	50.676	39.107	8.786	7.659	6.993	23.648
1000	-0.5	-0.5	0.0	4.744	51.881	38.974	8.510	7.599	6.954	23.671
1000	-0.5	-1.0	0.5	4.755	52.887	39.053	8.516	7.612	6.972	23.708
1000	-0.5	-1.5	1.0	4.749	54.034	39.207	8.509	7.600	6.950	23.803
1000	-0.5	0.5	-1.0	4.754	51.453	39.082	8.601	7.593	6.947	23.753
1000	-1.0	-1.0	0.0	4.763	56.310	39.106	8.595	7.621	6.977	23.723
1000	-1.0	-1.5	0.5	4.742	56.353	39.332	8.583	7.604	6.956	23.720
1000	-1.0	-2.0	1.0	4.763	58.429	39.281	8.807	7.623	6.970	23.598
1000	-1.0	1.0	-2.0	4.770	51.705	39.107	8.786	7.659	6.993	23.648
1000	-2.0	-2.0	0.0	4.744	56.868	38.974	8.510	7.599	6.954	23.671
1000	-2.0	-2.5	0.5	4.755	57.901	39.053	8.516	7.612	6.972	23.708
1000	-2.0	-3.0	1.0	4.749	58.927	39.207	8.509	7.600	6.950	23.803
1000	-2.0	2.0	-4.0	4.754	53.026	39.082	8.601	7.593	6.947	23.753
5000	0.0	0.0	0.0	4.737	49.746	45.099	8.284	8.010	7.597	25.263
5000	0.0	-0.5	0.5	4.715	50.373	44.915	8.347	8.010	7.578	25.245
5000	0.0	-1.0	1.0	4.738	53.318	44.801	8.282	7.989	7.576	25.336
5000	0.0	0.0	0.0	4.739	49.353	44.842	8.280	7.999	7.593	25.419
5000	-0.5	-0.5	0.0	4.722	51.752	44.849	8.351	7.980	7.561	25.400
5000	-0.5	-1.0	0.5	4.726	52.430	44.809	8.509	8.018	7.597	25.205
5000	-0.5	-1.5	1.0	4.740	52.824	45.025	8.344	8.006	7.578	25.375
5000	-0.5	0.5	-1.0	4.688	50.063	45.025	8.266	7.979	7.553	25.191
5000	-1.0	-1.0	0.0	4.737	52.779	45.099	8.284	8.010	7.597	25.263
5000	-1.0	-1.5	0.5	4.715	53.331	44.915	8.347	8.010	7.578	25.245
5000	-1.0	-2.0	1.0	4.738	56.566	44.801	8.282	7.989	7.576	25.336
5000	-1.0	1.0	-2.0	4.739	50.196	44.842	8.280	7.999	7.593	25.419
5000	-2.0	-2.0	0.0	4.722	56.375	44.849	8.351	7.980	7.561	25.400
5000	-2.0	-2.5	0.5	4.726	57.523	44.809	8.509	8.018	7.597	25.205
5000	-2.0	-3.0	1.0	4.740	57.623	45.025	8.344	8.006	7.578	25.375
5000	-2.0	2.0	-4.0	4.688	51.631	45.025	8.266	7.979	7.553	25.191

Parameters for binary outcomes

Web Table 2: Parameter values for the simulation study for binary outcomes.

$\mu(1,1)$	$\gamma_{1,1}$	$\mu(0,1)$	$\gamma_{0,1}$	$ATE(S=1)$	$\mu(1,0)$	$\gamma_{1,0}$	$\mu(0,0)$	$\gamma_{0,0}$	$ATE(S=0)$	$dATE$
0.7	1.614	0.7	1.614	0	0.6	0.823	0.6	0.823	0	0
0.7	1.614	0.7	1.614	0	0.5	0.002	0.6	0.823	-0.1	0.1
0.7	1.614	0.7	1.614	0	0.4	-0.823	0.6	0.823	-0.2	0.2
0.7	1.614	0.7	1.614	0	0.6	0.823	0.6	0.823	0	0
0.6	0.781	0.7	1.614	-0.1	0.5	0.002	0.6	0.823	-0.1	0
0.6	0.781	0.7	1.614	-0.1	0.4	-0.823	0.6	0.823	-0.2	0.1
0.6	0.781	0.7	1.614	-0.1	0.3	-1.702	0.6	0.823	-0.3	0.2
0.6	0.781	0.7	1.614	-0.1	0.7	1.703	0.6	0.823	0.1	-0.2
0.5	0.000	0.7	1.614	-0.2	0.4	-0.823	0.6	0.823	-0.2	0
0.5	0.000	0.7	1.614	-0.2	0.3	-1.702	0.6	0.823	-0.3	0.1
0.5	0.000	0.7	1.614	-0.2	0.2	-2.739	0.6	0.823	-0.4	0.2
0.5	0.000	0.7	1.614	-0.2	0.8	2.737	0.6	0.823	0.2	-0.4
0.4	-0.779	0.7	1.614	-0.3	0.3	-1.702	0.6	0.823	-0.3	0
0.4	-0.779	0.7	1.614	-0.3	0.2	-2.739	0.6	0.823	-0.4	0.1
0.4	-0.779	0.7	1.614	-0.3	0.1	-4.181	0.6	0.823	-0.5	0.2
0.4	-0.779	0.7	1.614	-0.3	0.9	4.180	0.6	0.823	0.3	-0.6

We numerically solved for $\gamma_{a,s}$, the intercept in the treatment and subgroup specific model for the outcome, that resulted in the desired subgroup-specific marginal mean $\mu(a,s)$. The mean difference of stratum s is $ATE(S=s)$, so $ATE(S=s) = \mu(1,s) - \mu(0,s)$; $dATE = ATE(S=1) - ATE(S=0)$.

Simulation results for binary outcomes

Correlated baseline covariates when $\Pr[S=1|X]=0.5$

Web Table 3: Bias multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	$ATE(S=1)$	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	-0.005	-0.158	-1.919	0.032	0.004	-0.006	-0.887
500	0.0	-0.5	0.5	-0.000	-0.044	-1.848	0.020	0.014	0.010	-0.904
500	0.0	-1.0	1.0	-0.004	-0.362	-1.859	-0.026	-0.014	-0.008	-0.819
500	0.0	0.0	0.0	0.015	-0.028	-1.795	0.029	0.027	0.019	-0.957
500	-0.5	-0.5	0.0	0.009	0.100	-1.651	0.004	0.004	-0.000	-0.780
500	-0.5	-1.0	0.5	-0.013	-0.227	-1.823	-0.020	-0.006	-0.004	-0.907
500	-0.5	-1.5	1.0	0.017	0.202	-1.575	0.031	0.024	0.017	-0.859
500	-0.5	0.5	-1.0	-0.031	0.047	-1.834	-0.044	-0.041	-0.032	-0.984
500	-1.0	-1.0	0.0	-0.005	-0.178	-1.919	0.032	0.004	-0.006	-0.887
500	-1.0	-1.5	0.5	-0.000	-0.067	-1.848	0.020	0.014	0.010	-0.904
500	-1.0	-2.0	1.0	-0.004	-0.403	-1.859	-0.026	-0.014	-0.008	-0.819
500	-1.0	1.0	-2.0	0.015	0.010	-1.795	0.029	0.027	0.019	-0.957
500	-2.0	-2.0	0.0	0.009	0.096	-1.651	0.004	0.004	-0.000	-0.780
500	-2.0	-2.5	0.5	-0.013	-0.260	-1.823	-0.020	-0.006	-0.004	-0.907
500	-2.0	-3.0	1.0	0.017	0.224	-1.575	0.031	0.024	0.017	-0.859
500	-2.0	2.0	-4.0	-0.031	0.103	-1.834	-0.044	-0.041	-0.032	-0.984
1000	0.0	0.0	0.0	0.000	-0.175	-1.770	0.005	0.002	0.002	-1.015
1000	0.0	-0.5	0.5	0.013	-0.124	-1.775	0.042	0.033	0.030	-1.045
1000	0.0	-1.0	1.0	-0.001	-0.104	-1.638	-0.035	-0.025	-0.021	-1.023
1000	0.0	0.0	0.0	0.004	-0.074	-1.653	-0.031	-0.010	-0.001	-1.000
1000	-0.5	-0.5	0.0	0.036	-0.090	-1.708	0.019	0.018	0.017	-1.002
1000	-0.5	-1.0	0.5	-0.008	-0.150	-1.748	-0.052	-0.024	-0.008	-0.890
1000	-0.5	-1.5	1.0	-0.006	-0.207	-1.878	0.003	-0.005	-0.009	-1.085
1000	-0.5	0.5	-1.0	-0.002	-0.009	-1.665	0.011	0.011	0.009	-0.978
1000	-1.0	-1.0	0.0	0.000	-0.210	-1.770	0.005	0.002	0.002	-1.015
1000	-1.0	-1.5	0.5	0.013	-0.138	-1.775	0.042	0.033	0.030	-1.045
1000	-1.0	-2.0	1.0	-0.001	-0.107	-1.638	-0.035	-0.025	-0.021	-1.023
1000	-1.0	1.0	-2.0	0.004	-0.052	-1.653	-0.031	-0.010	-0.001	-1.000
1000	-2.0	-2.0	0.0	0.036	-0.105	-1.708	0.019	0.018	0.017	-1.002
1000	-2.0	-2.5	0.5	-0.008	-0.177	-1.748	-0.052	-0.024	-0.008	-0.890
1000	-2.0	-3.0	1.0	-0.006	-0.247	-1.878	0.003	-0.005	-0.009	-1.085
1000	-2.0	2.0	-4.0	-0.002	0.033	-1.665	0.011	0.011	0.009	-0.978
5000	0.0	0.0	0.0	0.023	0.187	-1.000	0.007	0.013	0.013	-1.115
5000	0.0	-0.5	0.5	-0.015	-0.060	-1.198	-0.056	-0.055	-0.055	-1.301
5000	0.0	-1.0	1.0	0.008	0.292	-0.934	0.030	0.026	0.021	-1.100
5000	0.0	0.0	0.0	0.002	0.373	-0.846	-0.007	-0.002	-0.005	-1.176
5000	-0.5	-0.5	0.0	0.015	-0.083	-1.211	0.055	0.056	0.056	-1.207
5000	-0.5	-1.0	0.5	0.026	0.080	-1.046	0.033	0.034	0.035	-1.213
5000	-0.5	-1.5	1.0	-0.001	0.064	-1.088	-0.011	-0.008	-0.007	-1.132
5000	-0.5	0.5	-1.0	0.003	0.073	-1.207	-0.031	-0.025	-0.020	-1.333
5000	-1.0	-1.0	0.0	0.023	0.183	-1.000	0.007	0.013	0.013	-1.115
5000	-1.0	-1.5	0.5	-0.015	-0.060	-1.198	-0.056	-0.055	-0.055	-1.301
5000	-1.0	-2.0	1.0	0.008	0.292	-0.934	0.030	0.026	0.021	-1.100
5000	-1.0	1.0	-2.0	0.002	0.382	-0.846	-0.007	-0.002	-0.005	-1.176
5000	-2.0	-2.0	0.0	0.015	-0.091	-1.211	0.055	0.056	0.056	-1.207
5000	-2.0	-2.5	0.5	0.026	0.101	-1.046	0.033	0.034	0.035	-1.213
5000	-2.0	-3.0	1.0	-0.001	0.056	-1.088	-0.011	-0.008	-0.007	-1.132
5000	-2.0	2.0	-4.0	0.003	0.070	-1.207	-0.031	-0.025	-0.020	-1.333

Web Table 4: Standard deviation multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	$ATE(S=1)$	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	4.293	65.082	34.936	9.002	6.845	6.098	19.082
500	0.0	-0.5	0.5	4.310	69.719	34.653	9.037	6.860	6.128	19.139
500	0.0	-1.0	1.0	4.318	57.310	34.720	8.601	6.866	6.128	19.284
500	0.0	0.0	0.0	4.310	56.995	34.679	8.913	6.842	6.106	19.276
500	-0.5	-0.5	0.0	4.301	60.684	34.619	8.560	6.844	6.112	19.207
500	-0.5	-1.0	0.5	4.303	61.682	34.717	8.597	6.858	6.126	19.227
500	-0.5	-1.5	1.0	4.311	62.521	34.833	8.818	6.862	6.129	19.169
500	-0.5	0.5	-1.0	4.313	60.770	34.453	8.800	6.857	6.136	19.209
500	-1.0	-1.0	0.0	4.293	68.675	34.936	9.002	6.845	6.098	19.082
500	-1.0	-1.5	0.5	4.310	72.687	34.653	9.037	6.860	6.128	19.139
500	-1.0	-2.0	1.0	4.318	61.043	34.720	8.601	6.866	6.128	19.284
500	-1.0	1.0	-2.0	4.310	55.879	34.679	8.913	6.842	6.106	19.276
500	-2.0	-2.0	0.0	4.301	66.941	34.619	8.560	6.844	6.112	19.207
500	-2.0	-2.5	0.5	4.303	66.772	34.717	8.597	6.858	6.126	19.227
500	-2.0	-3.0	1.0	4.311	68.604	34.833	8.818	6.862	6.129	19.169
500	-2.0	2.0	-4.0	4.313	58.088	34.453	8.800	6.857	6.136	19.209
1000	0.0	0.0	0.0	4.284	53.797	38.096	8.587	7.139	6.434	19.639
1000	0.0	-0.5	0.5	4.273	54.578	38.433	8.348	7.147	6.408	19.669
1000	0.0	-1.0	1.0	4.271	53.107	37.860	8.281	7.106	6.399	19.669
1000	0.0	0.0	0.0	4.279	52.337	37.858	8.573	7.137	6.416	19.734
1000	-0.5	-0.5	0.0	4.275	58.404	38.090	8.510	7.153	6.419	19.692
1000	-0.5	-1.0	0.5	4.288	54.868	37.996	8.280	7.152	6.436	19.685
1000	-0.5	-1.5	1.0	4.258	58.756	38.113	8.460	7.113	6.387	19.713
1000	-0.5	0.5	-1.0	4.271	51.725	37.988	8.380	7.156	6.425	19.683
1000	-1.0	-1.0	0.0	4.284	57.023	38.096	8.587	7.139	6.434	19.639
1000	-1.0	-1.5	0.5	4.273	58.072	38.433	8.348	7.147	6.408	19.669
1000	-1.0	-2.0	1.0	4.271	56.418	37.860	8.281	7.106	6.399	19.669
1000	-1.0	1.0	-2.0	4.279	51.646	37.858	8.573	7.137	6.416	19.734
1000	-2.0	-2.0	0.0	4.275	63.542	38.090	8.510	7.153	6.419	19.692
1000	-2.0	-2.5	0.5	4.288	60.071	37.996	8.280	7.152	6.436	19.685
1000	-2.0	-3.0	1.0	4.258	64.154	38.113	8.460	7.113	6.387	19.713
1000	-2.0	2.0	-4.0	4.271	50.757	37.988	8.380	7.156	6.425	19.683
5000	0.0	0.0	0.0	4.258	51.604	44.757	8.093	7.640	7.074	21.013
5000	0.0	-0.5	0.5	4.255	52.400	44.692	8.200	7.658	7.070	21.091
5000	0.0	-1.0	1.0	4.272	56.201	45.191	8.209	7.668	7.075	20.974
5000	0.0	0.0	0.0	4.261	55.878	44.743	8.221	7.610	7.069	20.992
5000	-0.5	-0.5	0.0	4.270	53.269	44.776	8.039	7.607	7.069	21.032
5000	-0.5	-1.0	0.5	4.247	53.511	44.611	8.061	7.602	7.047	20.993
5000	-0.5	-1.5	1.0	4.259	54.813	44.634	8.049	7.624	7.076	21.004
5000	-0.5	0.5	-1.0	4.259	54.291	45.090	8.186	7.655	7.075	21.068
5000	-1.0	-1.0	0.0	4.258	54.576	44.757	8.093	7.640	7.074	21.013
5000	-1.0	-1.5	0.5	4.255	55.643	44.692	8.200	7.658	7.070	21.091
5000	-1.0	-2.0	1.0	4.272	59.554	45.191	8.209	7.668	7.075	20.974
5000	-1.0	1.0	-2.0	4.261	55.049	44.743	8.221	7.610	7.069	20.992
5000	-2.0	-2.0	0.0	4.270	58.372	44.776	8.039	7.607	7.069	21.032
5000	-2.0	-2.5	0.5	4.247	58.404	44.611	8.061	7.602	7.047	20.993
5000	-2.0	-3.0	1.0	4.259	59.817	44.634	8.049	7.624	7.076	21.004
5000	-2.0	2.0	-4.0	4.259	52.565	45.090	8.186	7.655	7.075	21.068

Independent baseline covariates

Independent baseline covariates when $\Pr[S=1|X]=0.25$

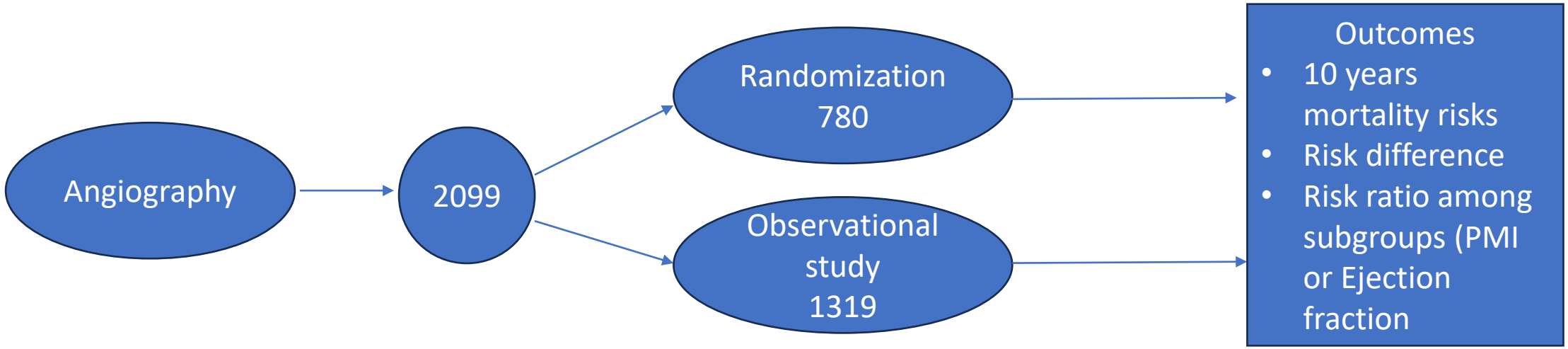
Web Table 5: Bias multiplied by $\sqrt{n}$ for estimators of $dATE$.

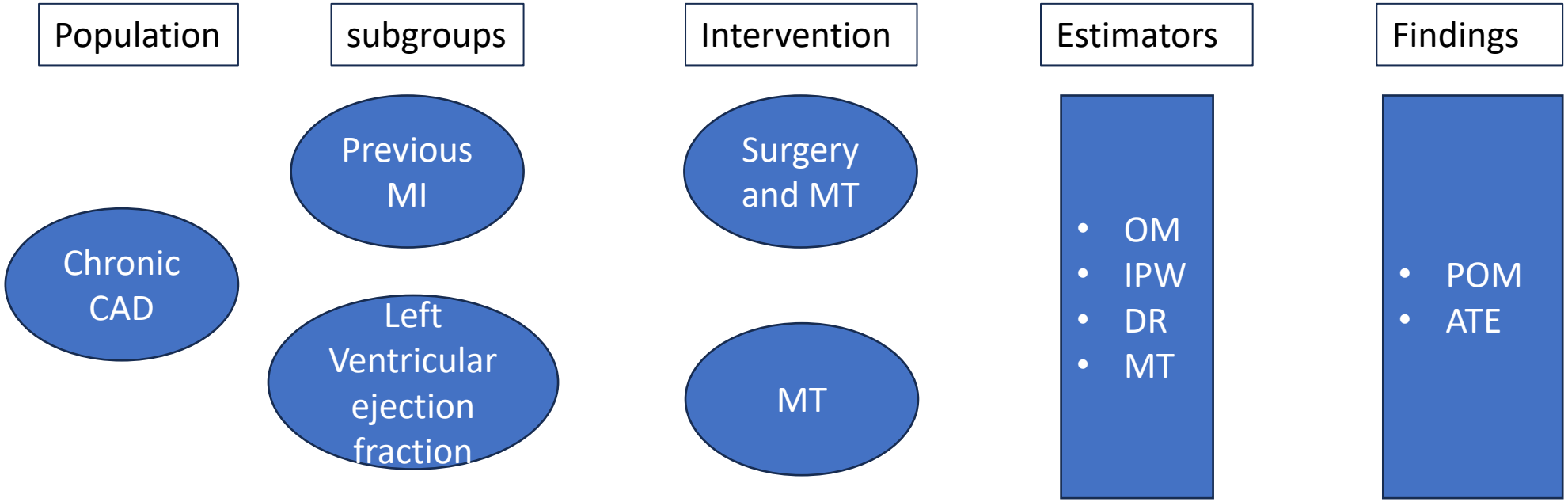
n	$ATE(S=1)$	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	-0.007	1.166	3.223	-0.024	-0.015	-0.013	2.232
500	0.0	-0.5	0.5	0.003	1.622	3.477	0.036	0.030	0.024	2.422
500	0.0	-1.0	1.0	0.017	1.171	3.279	0.035	0.027	0.027	2.463
500	0.0	0.0	0.0	-0.007	1.411	3.364	-0.007	-0.012	-0.019	2.481
500	-0.5	-0.5	0.0	0.002	1.079	3.295	-0.004	-0.000	-0.004	2.432
500	-0.5	-1.0	0.5	-0.019	1.129	3.310	-0.082	-0.055	-0.050	2.532
500	-0.5	-1.5	1.0	0.002	1.275	3.292	-0.012	-0.014	-0.008	2.480
500	-0.5	0.5	-1.0	-0.005	1.483	3.415	0.015	0.008	0.007	2.490
500	-1.0	-1.0	0.0	-0.007	1.307	3.223	-0.024	-0.015	-0.013	2.232
500	-1.0	-1.5	0.5	0.003	1.774	3.477	0.036	0.030	0.024	2.422
500	-1.0	-2.0	1.0	0.017	1.290	3.279	0.035	0.027	0.027	2.463
500	-1.0	1.0	-2.0	-0.007	1.470	3.364	-0.007	-0.012	-0.019	2.481
500	-2.0	-2.0	0.0	0.002	1.269	3.295	-0.004	-0.000	-0.004	2.432
500	-2.0	-2.5	0.5	-0.019	1.312	3.310	-0.082	-0.055	-0.050	2.532
500	-2.0	-3.0	1.0	0.002	1.454	3.292	-0.012	-0.014	-0.008	2.480
500	-2.0	2.0	-4.0	-0.005	1.574	3.415	0.015	0.008	0.007	2.490
1000	0.0	0.0	0.0	0.019	1.023	2.539	0.049	0.045	0.043	1.983
1000	0.0	-0.5	0.5	0.007	0.729	2.345	0.021	0.018	0.016	2.034
1000	0.0	-1.0	1.0	0.026	0.630	2.234	0.002	-0.016	-0.025	2.059
1000	0.0	0.0	0.0	0.011	0.842	2.458	0.014	-0.001	-0.006	2.047
1000	-0.5	-0.5	0.0	0.027	0.891	2.480	0.045	0.039	0.038	2.043
1000	-0.5	-1.0	0.5	0.002	1.213	2.692	0.019	0.026	0.020	2.127
1000	-0.5	-1.5	1.0	-0.010	0.986	2.532	0.025	0.026	0.025	2.148
1000	-0.5	0.5	-1.0	-0.022	1.066	2.569	-0.023	-0.018	-0.015	2.156
1000	-1.0	-1.0	0.0	0.019	1.128	2.535	0.049	0.045	0.043	1.983
1000	-1.0	-1.5	0.5	0.001	0.797	2.345	0.021	0.018	0.016	2.034
1000	-1.0	-2.0	1.0	-0.026	0.698	2.234	0.002	-0.016	-0.025	2.059
1000	-1.0	1.0	-2.0	-0.011	0.899	2.458	0.014	-0.001	-0.006	2.047
1000	-2.0	-2.0	0.0	0.027	1.035	2.480	0.045	0.039	0.038	2.043
1000	-2.0	-2.5	0.5	0.002	1.379	2.692	0.019	0.026	0.020	2.127
1000	-2.0	-3.0	1.0	-0.010	1.119	2.532	0.025	0.026	0.025	2.148
1000	-2.0	2.0	-4.0	-0.022	1.180	2.569	-0.023	-0.018	-0.015	2.156
5000	0.0	0.0	0.0	0.023	0.239	1.076	0.033	0.033	0.029	1.327
5000	0.0	-0.5	0.5	0.015	0.433	1.219	0.036	0.038	0.038	1.508
5000	0.0	-1.0	1.0	0.008	0.250	1.003	0.007	0.006	0.000	1.571
5000	0.0	0.0	0.0	0.023	0.366	1.136	0.038	0.039	0.039	1.505
5000	-0.5	-0.5	0.0	-0.013	0.184	1.030	-0.013	-0.017	-0.021	1.403
5000	-0.5	-1.0	0.5	0.006	0.570	1.299	0.003	0.012	0.014	1.484
5000	-0.5	-1.5	1.0	0.032	0.156	0.965	-0.019	-0.014	-0.011	1.441
5000	-0.5	0.5	-1.0	-0.024	0.420	1.184	-0.015	-0.017	-0.023	1.349
5000	-1.0	-1.0	0.0	0.023	0.265	1.076	0.033	0.033	0.029	1.327
5000	-1.0	-1.5	0.5	0.015	0.479	1.219	0.036	0.038	0.038	1.508
5000	-1.0	-2.0	1.0	0.008	0.285	1.003	0.007	0.006	0.000	1.571
5000	-1.0	1.0	-2.0	0.023	0.386	1.136	0.038	0.039	0.039	1.505
5000	-2.0	-2.0	0.0	-0.013	0.239	1.030	-0.013	-0.017	-0.021	1.403
5000	-2.0	-2.5	0.5	0.006	0.655	1.299	0.003	0.012	0.014	1.484
5000	-2.0	-3.0	1.0	0.032	0.212	0.965	-0.019	-0.014	-0.011	1.441
5000	-2.0	2.0	-4.0	-0.024	0.434	1.184	-0.015	-0.017	-0.023	1.349

Web Table 6: Standard deviation multiplied by $\sqrt{n}$ for estimators of $dATE$.

n	ATE(S=1)	$ATE(S=0)$	$dATE$	OM	IPW1	IPW2	DR1	DR2	DR3	MT
500	0.0	0.0	0.0	4.796	53.787	35.779	9.013	7.352	6.661	22.920
500	0.0	-0.5	0.5	4.798	57.128	35.693	8.972	7.380	6.690	22.837
500	0.0	-1.0	1.0	4.798	59.536	36.000	9.725	7.368	6.662	22.989
500	0.0	0.0	0.0	4.813	56.226	36.205	8.957	7.401	6.697	22.987
500	-0.5	-0.5	0.0	4.813	58.907	35.999	8.949	7.371	6.690	22.946
500	-0.5	-1.0	0.5	4.813	58.289	35.869	8.770	7.388	6.711	22.976
500	-0.5	-1.5	1.0	4.810	62.982	35.930	9.146	7.355	6.676	22.938
500	-0.5	0.5	-1.0	4.787	57.881	35.969	8.881	7.353	6.668	22.899
500	-1.0	-1.0	0.0	4.795	57.169	35.779	9.013	7.352	6.661	22.920
500	-1.0	-1.5	0.5	4.798	60.550	35.693	8.972	7.380	6.690	22.837
500	-1.0	-2.0	1.0	4.798	63.185	36.000	9.725	7.368	6.662	22.989
500	-1.0	1.0	-2.0	4.813	57.195	36.205	8.957	7.401	6.697	22.987
500	-2.0	-2.0	0.0	4.813	64.294	35.999	8.949	7.371	6.690	22.946
500	-2.0	-2.5	0.5	4.813	63.893	35.869	8.770	7.388	6.711	22.976
500	-2.0	-3.0	1.0	4.810	69.368	35.930	9.146	7.355	6.676	22.938
500	-2.0	2.0	-4.0	4.787	59.964	35.969	8.881	7.353	6.668	22.899
1000	0.0	0.0	0.0	4.763	53.143	39.106	8.595	7.621	6.977	23.723
1000	0.0	-0.5	0.5	4.742	52.963	39.332	8.583	7.604	6.956	23.720
1000	0.0	-1.0	1.0	4.763	55.256	39.281	8.807	7.623	6.970	23.598
1000	0.0	0.0	0.0	4.770	50.676	39.107	8.786	7.659	6.993	23.648
1000	-0.5	-0.5	0.0	4.744	51.881	38.974	8.510	7.599	6.954	23.671
1000	-0.5	-1.0	0.5	4.755	52.887	39.053	8.516	7.612	6.972	23.708
1000	-0.5	-1.5	1.0	4.749	54.034	39.207	8.509	7.600	6.950	23.803
1000	-0.5	0.5	-1.0	4.754	51.453	39.082	8.601	7.593	6.947	23.753
1000	-1.0	-1.0	0.0	4.763	56.310	39.106	8.595	7.621	6.977	23.723
1000	-1.0	-1.5	0.5	4.742	56.353	39.332	8.583	7.604	6.956	23.720
1000	-1.0	-2.0	1.0	4.763	58.429	39.281	8.807	7.623	6.970	23.598
1000	-1.0	1.0	-2.0	4.770	51.705	39.107	8.786	7.659	6.993	23.648
1000	-2.0	-2.0	0.0	4.744	56.868	38.974	8.510	7.599	6.954	23.671
1000	-2.0	-2.5	0.5	4.755	57.901	39.053	8.516	7.612	6.972	23.708
1000	-2.0	-3.0	1.0	4.749	58.927	39.207	8.509	7.600	6.950	23.803
1000	-2.0	2.0	-4.0	4.754	53.026	39.082	8.601	7.593	6.947	23.753
5000	0.0	0.0	0.0	4.737	49.746	45.099	8.284	8.010	7.597	25.263
5000	0.0	-0.5	0.5	4.715	50.373	44.915	8.347	8.010	7.578	25.245
5000	0.0	-1.0	1.0	4.738	53.318	44.801	8.282	7.989	7.576	25.336
5000	0.0	0.0	0.0	4.739	49.353	44.842	8.280	7.999	7.593	25.419
5000	-0.5	-0.5	0.0	4.722	51.752	44.849	8.351	7.980	7.561	25.400
5000	-0.5	-1.0	0.5	4.726	52.430	44.809	8.509	8.018	7.597	25.205
5000	-0.5	-1.5	1.0	4.740	52.824	45.025	8.344	8.006	7.578	25.375
5000	-0.5	0.5	-1.0	4.688	50.063	45.025	8.266	7.979	7.553	25.191
5000	-1.0	-1.0	0.0	4.737	52.779	45.099	8.284	8.010	7.597	25.263
5000	-1.0	-1.5	0.5	4.715	53.331	44.915	8.347	8.010	7.578	25.245
5000	-1.0	-2.0	1.0	4.738	56.566	44.801	8.282	7.989	7.576	25.336
5000	-1.0	1.0	-2.0	4.739	50.196	44.842	8.280	7.999	7.593	25.419
5000	-2.0	-2.0	0.0	4.722	56.375	44.849	8.351	7.980	7.561	25.400
5000	-2.0	-2.5	0.5	4.726	57.523	44.809	8.509	8.018	7.597	25.205
5000	-2.0	-3.0	1.0	4.740	57.623	45.025	8.344	8.006	7.578	25.375
5000	-2.0	2.0	-4.0	4.688	51.631	45.025	8.266	7.979	7.553	25.191

Coronary Artery Surgery Study (CASS) (August 1975 – December 1996)





Abbreviations: CAD; coronary artery disease; MI; myocardial infarction; MT; medical therapy; OM; outcome model; IPW; Inverse probability weighting; DR; doubly robust; MT; matching; POM; potential outcome mean; ATE; average treatment effects

Baseline covariates

Web Table 21: Baseline covariates in the CASS study.[a]

Variable	Levels	Non-randomized group		Randomized group	
		Surgery ($n = 430$)	Medical therapy ($n = 525$)	Surgery ($n = 368$)	Medical therapy ($n = 363$)
Age, years		51.3 (7.7)	50.6 (7.8)	51.4 (7.2)	50.9 (7.4)
Angina	None	70 (16.3%)	125 (23.8%)	83 (22.6%)	81 (22.3%)
	Present	360 (83.7%)	400 (76.2%)	285 (77.4%)	282 (77.7%)
History of MI	No	194 (45.1%)	212 (40.4%)	159 (43.2%)	135 (37.2%)
	Yes	236 (54.9%)	313 (59.6%)	209 (56.8%)	228 (62.8%)
LAD % obstruction		48.2 (39.8)	31.7 (36.2)	36.4 (38.0)	34.9 (37.0)
Left ventricular score		7.1 (2.7)	7.1 (2.7)	7.4 (2.9)	7.3 (2.8)
Diseased vessels	0	113 (26.3%)	234 (44.6%)	146 (39.7%)	133 (36.6%)
	≥ 1	317 (73.7%)	291 (55.4%)	222 (60.3%)	230 (63.4%)
Ejection fraction, %		60.2 (12.0)	60.1 (12.5)	60.9 (13.0)	59.8 (12.8)

Abbreviations: CASS, Coronary Artery Surgery Study; n, sample size; LAD, left anterior descending coronary artery; MI, myocardial infarction; SD, standard deviation.

[a] Results presented as mean (SD) for continuous variables and count (%) for discrete variables.

CASS subgroup (Previous myocardial infarction) analysis

Web Table 22: Subgroup analysis in the CASS study for previous myocardial infarction ($S = 1$ if history of myocardial infarction; $S = 0$ otherwise).

Estimator	Effect in $S = 1$		Effect in $S = 0$		Comparison of effects	
	OR	95% CI[a]	OR	95% CI	ROR	95% CI
TRIAL	0.78	0.49, 1.21	1.13	0.56, 2.40	0.69	0.29, 1.56
OBS	0.82	0.54, 1.24	1.49	0.83, 2.77	0.55	0.26, 1.11
OM	0.78	0.52, 1.19	1.51	0.84, 2.84	0.52	0.24, 1.06
IPW1	0.76	0.49, 1.15	1.51	0.82, 2.92	0.50	0.23, 1.04
IPW2	0.76	0.50, 1.16	1.49	0.80, 2.86	0.51	0.23, 1.06
DR1	0.76	0.50, 1.15	1.49	0.80, 2.85	0.51	0.23, 1.07
DR2	0.76	0.50, 1.16	1.49	0.80, 2.85	0.51	0.23, 1.06
DR3	0.76	0.50, 1.16	1.49	0.81, 2.84	0.51	0.24, 1.06
MT	0.68	0.46, 1.30	1.29	0.76, 3.37	0.52	0.20, 1.20

Abbreviations: CI, confidence interval; OR, odds ratio; ROR, relative odds ratio; TRIAL, trial-only (unadjusted); OBS, observational (unadjusted); OM, outcome modeling (4); IPW1, inverse probability weighting (5); IPW2, inverse probability weighting (6); DR1, doubly robust (7); DR2, doubly robust (8); DR3, doubly robust (9); MT, matching (10).

[a] 95 percent percentile confidence intervals from 10,000 bootstrap resamples.

Table 3. Subgroup Analysis of Previous Myocardial Infarction (S = 1 if History of Myocardial Infarction; S = 0 Otherwise) in the Coronary Artery Surgery Study, August 1975–December 1996

Estimator[a]	Effect in S = 1		Effect in S = 0		Comparison of Effects	
	RD[b]	95% CI[c]	RD[b]	95% CI[c]	DRD	95% CI[c]
Trial (unadjusted)	−4.43	−12.13, 3.37	1.36	−6.22, 8.89	−5.78	−16.50, 4.92
Obs (unadjusted)	−3.52	−10.39, 3.73	4.66	−2.11, 11.58	−8.18	−17.97, 1.52
OM	−4.25	−11.19, 3.07	4.84	−2.07, 11.99	−9.10	−19.09, 0.86
IPW1	−4.89	−11.95, 2.55	4.59	−2.09, 11.50	−9.49	−19.59, 0.39
IPW2	−4.82	−11.79, 2.61	4.40	−2.31, 11.29	−9.21	−19.07, 0.64
DR1	−4.89	−11.82, 2.58	4.48	−2.40, 11.56	−9.36	−19.30, 0.64
DR2	−4.88	−11.80, 2.58	4.48	−2.38, 11.56	−9.37	−19.30, 0.62
DR3	−4.84	−11.70, 2.56	4.45	−2.32, 11.56	−9.29	−19.17, 0.72
MT	−6.74	−12.93, 4.70	2.96	−2.97, 13.21	−9.70	−21.36, 2.61

Magnitude of effect heterogeneity across subgroups defined by previous MI was similar in observational and randomized components of CASS

CASS subgroup (ejection fraction ≥ 50%) analysis

Web Table 23: Subgroup analysis in the CASS study for ejection fraction ($S = 1$ if ejection fraction $\geq$50%; $S = 0$ otherwise).

Estimator	Effect in $S = 1$		Effect in $S = 0$		Comparison of effects	
	OR	95% CI[a]	OR	95% CI	ROR	95% CI
TRIAL	1.15	0.74, 1.82	0.40	0.18, 0.80	2.89	1.25, 7.25
OBS	1.14	0.76, 1.71	0.67	0.36, 1.24	1.70	0.81, 3.64
OM	1.11	0.74, 1.67	0.59	0.30, 1.10	1.88	0.89, 4.20
IPW1	1.11	0.74, 1.68	0.62	0.31, 1.23	1.80	0.80, 4.03
IPW2	1.11	0.73, 1.68	0.63	0.31, 1.22	1.77	0.81, 4.00
DR1	1.11	0.73, 1.67	0.62	0.31, 1.20	1.79	0.82, 4.02
DR2	1.11	0.73, 1.67	0.62	0.31, 1.19	1.79	0.82, 4.03
DR3	1.11	0.73, 1.68	0.62	0.31, 1.16	1.80	0.85, 4.04
MT	1.20	0.70, 1.94	0.75	0.26, 1.40	1.60	0.72, 5.06

Abbreviations: CI, confidence interval; OR, odds ratio; ROR, relative odds ratio; TRIAL, trial-only (unadjusted); OBS, observational (unadjusted); OM, outcome modeling (4); IPW1, inverse probability weighting (5); IPW2, inverse probability weighting (6); DR1, doubly robust (7); DR2, doubly robust (8); DR3, doubly robust (9); MT, matching (10).

[a] 95 percent percentile confidence intervals from 10,000 bootstrap resamples.

Table 4. Subgroup Analysis for the Ejection Fraction (S = 1 if Ejection Fraction ≥ 50%; S = 0 Otherwise) in the Coronary Artery Surgery Study, August 1975–December 1996

Estimator[a]	Effect in $S = 1$		Effect in $S = 0$		Comparison of Effects	
	RD[b]	95% CI[c]	RD[b]	95% CI[c]	DRD	95% CI[c]
Trial (unadjusted)	1.89	−4.06, 7.75	−18.32	−32.02, −4.42	20.22	4.93, 35.15
Obs (unadjusted)	1.63	−3.31, 6.72	−9.15	−22.84, 5.00	10.78	−4.12, 25.52
OM	1.28	−3.78, 6.46	−12.06	−26.46, 2.19	13.35	−1.81, 28.76
IPW1	1.36	−3.80, 6.55	−11.11	−25.93, 4.87	12.46	−4.33, 28.26
IPW2	1.34	−3.84, 6.52	−10.81	−25.76, 4.74	12.14	−4.18, 28.19
DR1	1.28	−3.87, 6.47	−11.09	−25.70, 4.12	12.37	−3.75, 28.02
DR2	1.28	−3.87, 6.47	−11.08	−25.71, 3.99	12.36	−3.59, 28.02
DR3	1.31	−3.85, 6.51	−11.16	−25.75, 3.40	12.47	−2.85, 28.08
MT	2.32	−4.40, 8.53	−6.70	−29.01, 7.99	9.02	−6.90, 32.08

Magnitude of effect heterogeneity across subgroups defined by ejection fraction in observational components is smaller compared with randomized components of CASS

May be due to unmeasured confounding or due to differences in the distribution of effect modifiers other than ejection fraction

Conclusion

- Bias and standard deviation of sampling distributors of estimators vary substantially even under the best-case scenario (no confounding or unmeasured covariates and no model specification)
- Use multiple estimators in order to asses whether model specification choices influence results
- Doubly roboust is particularly attractive as it offers robustness against model specification
- Data adaptive methods (eg., machine learning methods) may be used to estimate the conditional expectation of the outcome or the probability of treatment in order to mitigate the risk of model specification


Thank you!