



INTRODUCTION

- Propensity score matching (PSM), a commonly used method for covariate balancing in causal inference research, is subject to limitations especially in studies with small sample sizes:
 - Insufficient observations to develop accurate propensity models
 - Potential bias and variance of estimates due to limited overlap of covariate distributions
- Cardinality matching (CM), an optimization algorithm, finds the largest matched sample meeting a set of prespecified balance criteria thereby overcoming the limitations of PSM.
- Prior research has shown large-scale CM to be associated with superior patient retention and comparable systematic bias as compared to large-scale PSM. However, large-scale methods may not be applicable in all settings.

STUDY OBJECTIVES

- To describe the performance of non-large-scale PSM and CM in terms of post-match patient retention, covariate balance and residual confounding at progressively smaller sample sizes.

METHODS

Study Design: Retrospective comparative new-user cohort study

Data Source: IBM® MarketScan® Commercial Claims and Encounters database, which contains patient health data from employers and health plans providing private insurance coverage

Study Population: We identified new users of β -blockers versus angiotensin-converting enzyme inhibitors (ACEI) monotherapy between 10-01-2014 and 01-01-2017 with a prior history of hypertension (index=first drug exposure)

Sample Groups: All analyses were conducted within 10% and 0.25% sample group consisting of 5 and 200 subsample draws, respectively

Performance criteria for comparison of PSM vs. CM: Post-match size, matching covariate balance, observed covariate balance, and expected absolute systematic error (EASE)

Statistical Analysis

- PSM:** Conducted through nearest-neighbor matching (1:1 match; caliper=0.15)
- CM:** Conducted through 1:1 matching and, in four separate analyses, with a pre-specified balance criterion permitting a maximum standardized mean difference (SMD) between study groups of 0, 0.01, 0.05, and 0.10
- Covariates:** 37 matching covariates for both PSM and CM, including patient demographics and select clinical characteristics
- Observed Covariates:** Patient demographics, and all observed prior conditions, drug exposures, and procedures
- Negative Control Outcomes:** 105 negative control outcome experiments perceived as unassociated with the treatment (i.e., true relative risk = 1) were used to compute the EASE. The 95% credible interval of differences in EASE between matching techniques were measured using a non-parametric bootstrap

RESULTS

Post-Match Results:

- A total of 185,235 (β -blocker: 56,872; ACEI: 129,363) patients meeting the study criteria were identified pre-match
 - 10% Sample Group:** 18,576 (β -blocker: 5,675; ACEI: 12,901)
 - 0.25% Sample Group:** 465 (β -blocker: 142; ACEI: 323)
- The average number of observed covariates was as follows
 - 10% Sample Group:** 35,584.8 (SD=687.7)
 - 0.25% Sample Group:** 8,550.7 (SD=413.0)

Post-Match Sample Size:

- Total post-match sample sizes are summarized in **Table 1**
- As compared to PSM, CM achieved superior post-match sample size at all pre-specified balance criteria.
- Stricter prespecified balance criteria were associated with a reduction in post-match sample size with CM

Table 1. Total post-match sample sizes

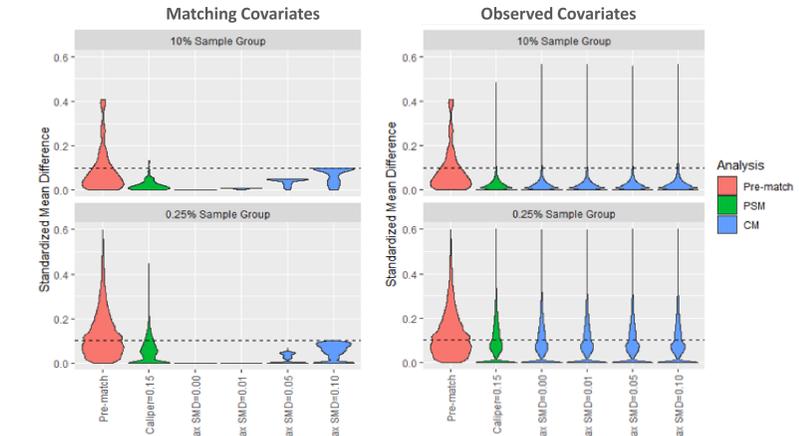
Matching Technique	10% Sample Group (Pre-match, N=18,576)	0.25% Sample Group (Pre-match, N=465)
PSM	9,833.8 (sd=142.7)	229.75 (sd=14.1)
CM, max SMD		
0.00	10,870.8 (sd=62.5)	254.76 (sd=10.3)
0.01	10,908.8 (sd=55.8)	254.76 (sd=10.3)
0.05	11,045 (sd=49.5)	259.21 (sd=9.3)
0.10	11,154 (sd=30.4)	268.65 (sd=7.3)

RESULTS

Post-Match Covariate Balance:

- Figure 1** provide a visual representation of the post-match probability distribution of SMDs of matching and observed covariates
- After PSM, an average of 1.6% and 15.3% of matching covariates were imbalanced (i.e., SMD >0.10) in the 10% and 0.25% sample groups, respectively; CM achieved covariate balance across all analyses
- Both pre- and post-match, observed covariate imbalance was higher in the 0.25% sample group as compared to the 10% sample group
- CM with stricter prespecified balance criteria had improved observed covariate balance. For instance, a 20.5% (2.8% vs. 3.4%) and 3.8% (16.3% vs. 16.9%) increase in the average frequency of observed covariate imbalance associated with CM requiring a SMD of 0 vs. 0.10 was identified in the 10% and 0.25% sample groups, respectively
- No significant differences in observed covariates were observed between PSM and CM

Figure 1. Violin plot of the post-match distribution of standardized mean differences of matching covariates (left) and observed covariates (right)



Post-Match Residual Confounding:

- Figure 2** shows the pre- and post-match EASE; and Table 2 shows the difference in EASE between matching techniques
- As compared to PSM, CM with more stringent balance criteria (<0.01) was associated with a significant reduction in EASE. For instance, comparing CM requiring a SMD of 0.01 vs. PSM:
 - 10% Sample Group:** 0.3 vs. 0.44, p=0.004
 - 0.25% Sample Group:** 0.3 vs. 0.38, p=0.031

Figure 2. Pre-match, post-PSM, and post-CM EASE)

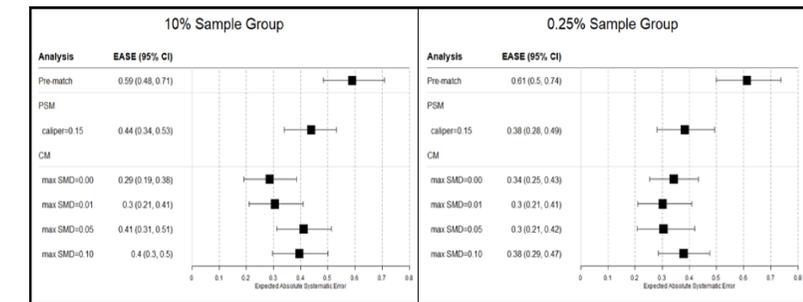


Table 2. Difference in EASE between matching techniques*

Sample Group	Matching Technique	PSM	CM, max SMD=0.00	CM, max SMD=0.01	CM, max SMD=0.05	CM, max SMD=0.10
10%	Pre-Match	0.15 (0.06, 0.28) p=0.003	0.31 (0.21, 0.4) p<0.001	0.28 (0.19, 0.38) p<0.001	0.18 (0.1, 0.27) p<0.001	0.2 (0.09, 0.29) p<0.001
	PSM		0.15 (0.06, 0.23) p=0.003	0.13 (0.06, 0.21) p=0.004	0.03 (-0.06, 0.1) p=0.202	0.04 (-0.09, 0.12) p=0.225
	CM, max SMD=0.00			-0.02 (-0.08, 0.06) p=0.283	-0.13 (-0.19, -0.06) p<0.001	-0.11 (-0.21, -0.06) p<0.001
	CM, max SMD=0.01				-0.11 (-0.18, -0.05) p=0.002	-0.08 (-0.21, -0.02) p=0.003
	CM, max SMD=0.05					0.02 (-0.1, 0.09) p=0.379
0.25%	Pre-Match	0.23 (0.14, 0.33) p<0.001	0.27 (0.19, 0.36) p<0.001	0.31 (0.22, 0.41) p<0.001	0.31 (0.2, 0.39) p<0.001	0.23 (0.15, 0.32) p<0.001
	PSM		0.04 (-0.02, 0.12) p=0.082	0.08 (0, 0.15) p=0.031	0.06 (-0.03, 0.15) p=0.062	-0.01 (-0.06, 0.08) p=0.482
	CM, max SMD=0.00			0.04 (-0.04, 0.09) p=0.155	0.03 (-0.07, 0.09) p=0.201	-0.05 (-0.1, 0.01) p=0.046
	CM, max SMD=0.01				-0.01 (-0.09, 0.05) p=0.404	-0.09 (-0.13, 0) p=0.022
	CM, max SMD=0.05					-0.08 (-0.13, 0.02) p=0.046

* Difference in EASE = (EASE of method in row) minus (EASE of method in column); positive values indicate increased systematic error among method listed in row, and vice versa

CONCLUSION

CM found the largest matched sample meeting a set of prespecified balance criteria. CM with stricter prespecified balance criteria was associated with improved residual confounding as compared to PSM. **We recommend considering CM with more stringent balance criteria as an alternative to PSM when using a small set of matching covariates.**