Beyond Traditional Randomization: Using Covariate Contained Randomization in Cluster Trials

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Cluster Randomized Trials

- Randomizing groups (clusters) instead of individuals
  - Schools, communities, hospitals, dialysis centres
  - Common in public health, education, and social science research
- Advantages: control for cluster-level factors, increase feasibility, and reduce contamination
- Disadvantages: Limited number of clusters available
  - Most CRTs randomize ≤ 24 clusters
  - High chance imbalance is likely to occur after simple randomization

Focus is on 2-arm parallel design trials where the intervention is implemented simultaneously for all clusters

Randomization in Experimental Designs

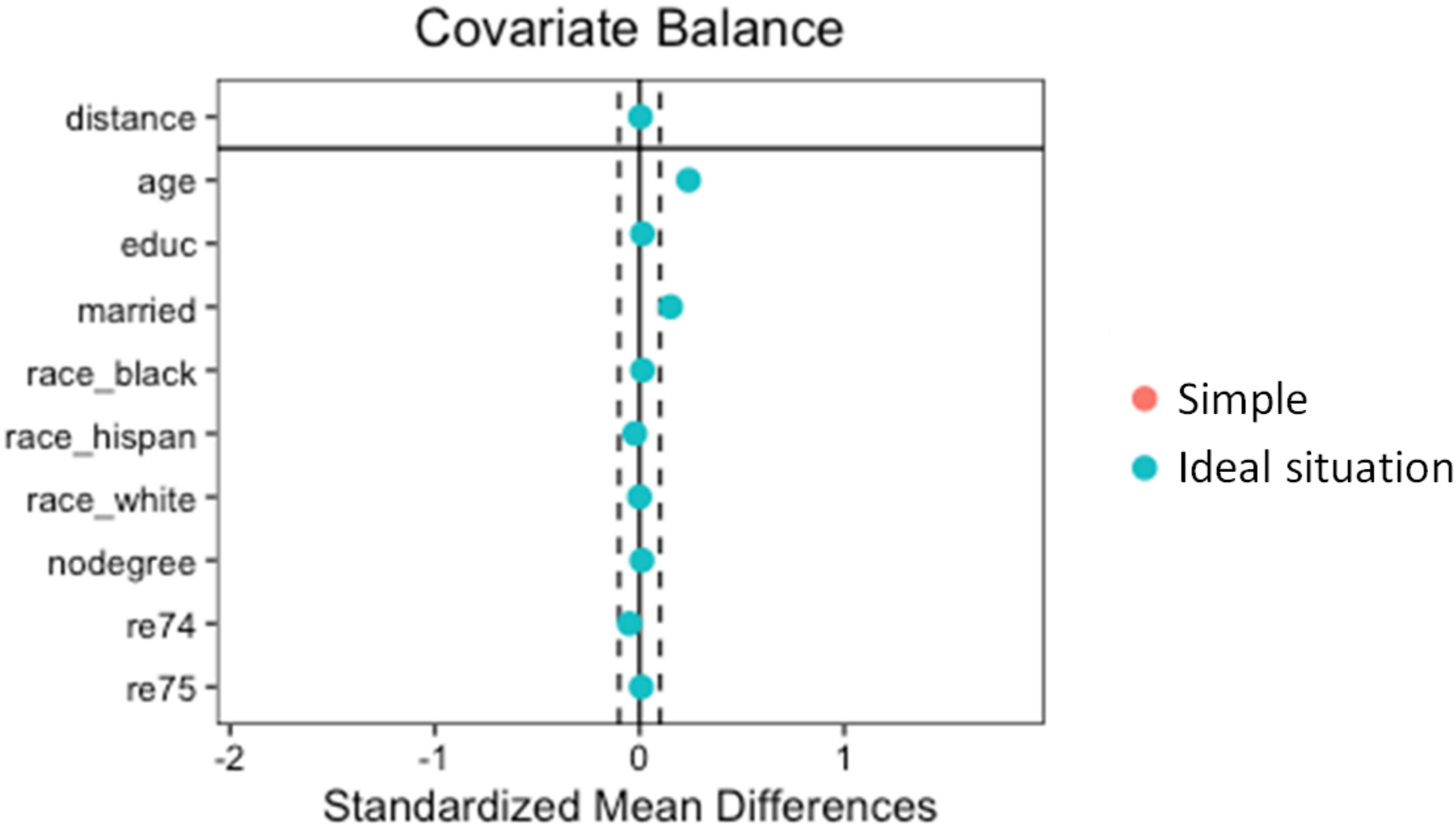
- Create comparable groups, control confounding, and minimize bias
- Simple randomization
- Constrained randomization
  - Stratification
  - Minimization
  - Adaptive randomization
  - Covariate constrained randomization

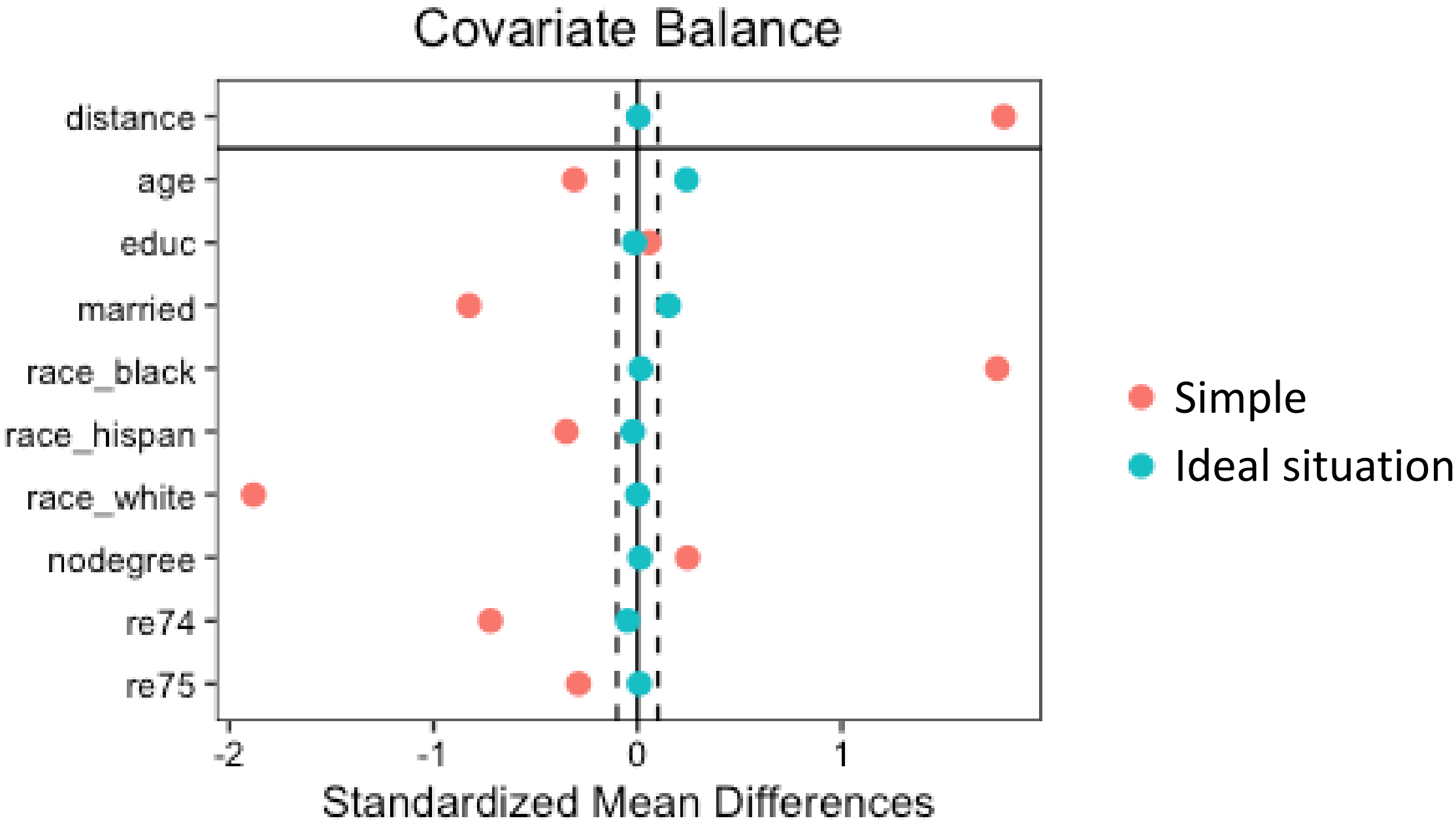
Covariate Imbalance in Cluster Randomized Trials

Covariate imbalance: when treatment groups differ systematically on baseline characteristics

Consequences: reduced statistical power, poor internal validity, incorrect conclusions

Simple randomization: may not adequately balance baseline covariates


Covariate Balance
distance
age
educ
married
race_black
race_hispan
race_white
nodegree
re74
re75
-2
-1
0
1
Standardized Mean Differences
Simple
Ideal situation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Covariate Constrained Randomization

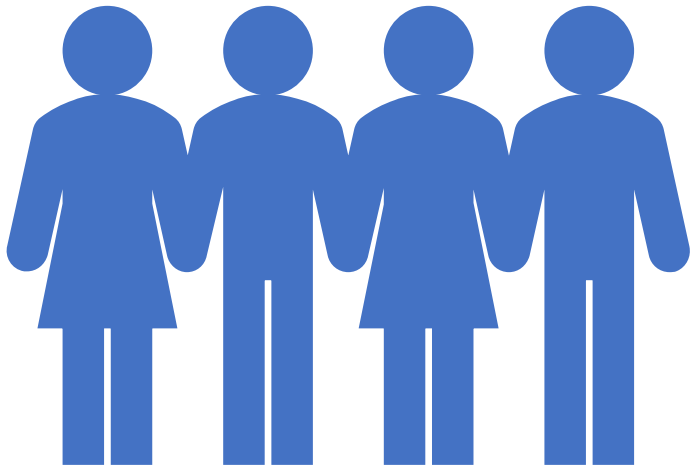
Aims to improve balance by restricting randomization to a subset of acceptable allocations

Selects allocations that satisfy predefined criteria for covariate balance

Algorithm

Step 1	Step 2	Step 3	Step 4	Step 5
Define a set of key covariates and balance criteria	Generate a large number of random allocations	Calculate distance metrics between treatment groups for each allocation	Select a subset of allocations that satisfy the balance criteria	Randomly choose one allocation from the subset as the final assignment

Implementation of CCR in Practice



- Considerations: sample size, number of covariates, desired balance threshold, and don’t over constraining the randomization
- Tips: perform a pilot study, use simulations to determine appropriate criteria, **collaborate with a statistician**

  https://t.ly/-24R

A motivating example

- 2-arm parallel CRT with 72 hemodialysis centres

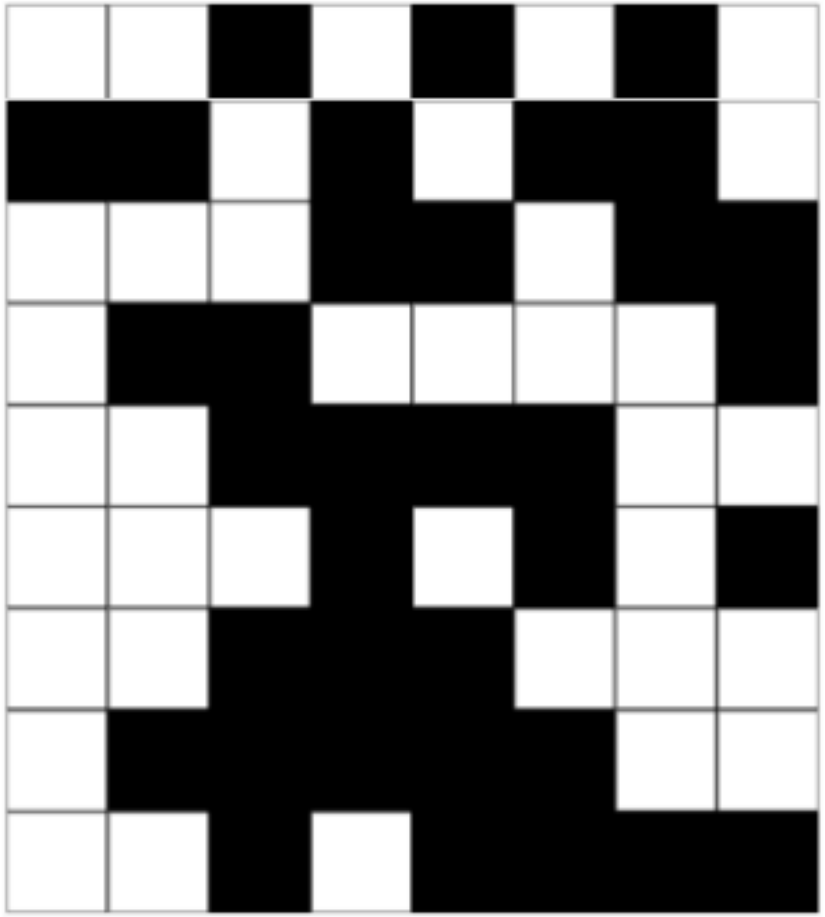
- Historical (1-year old) data is known for all hemodialysis centres

Randomization Procedures

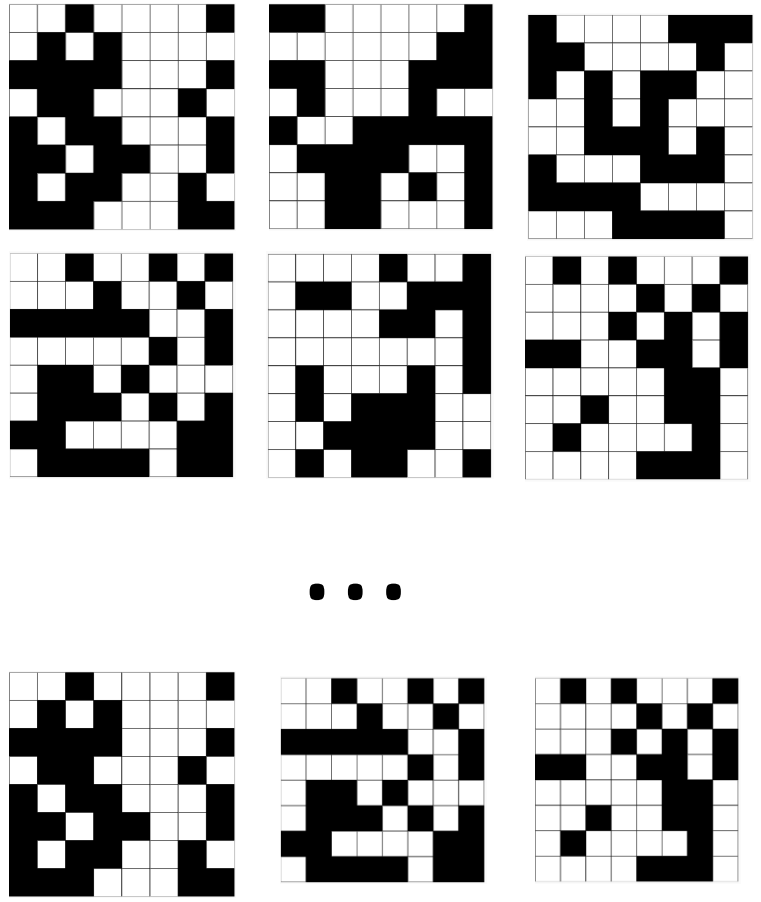
Simple

Prognostic factors

Covariate constrained randomization

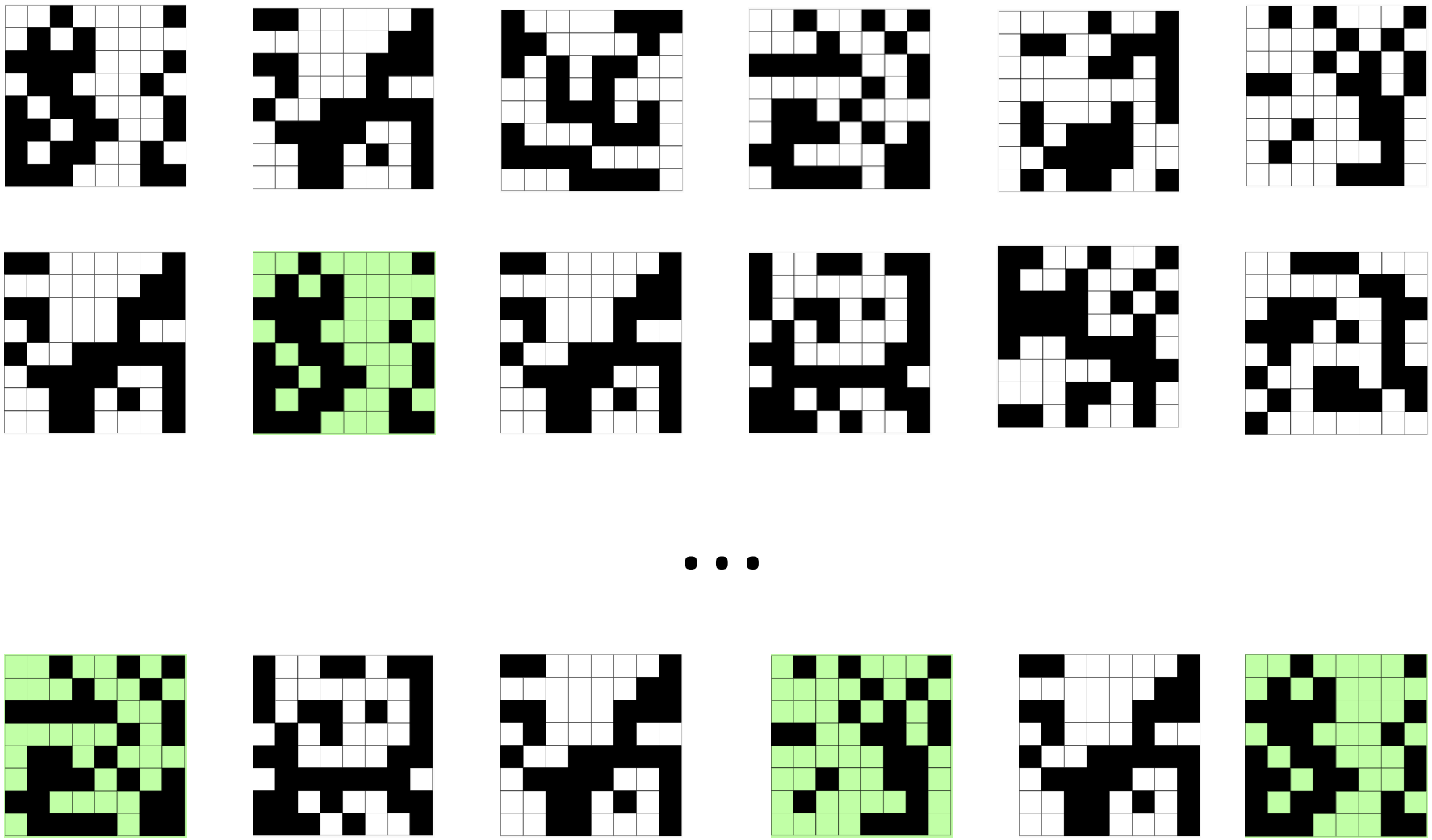


300,000 times

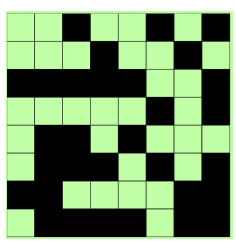
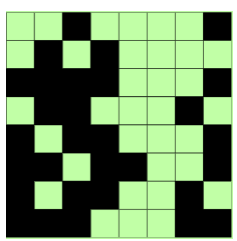
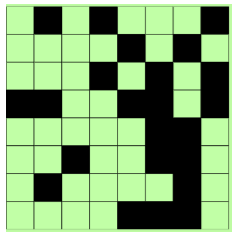
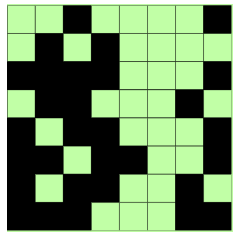


Variable	Control	Intervention	Standardized difference
Age, Mean ± SD	66.70 ± 14.78	66.21 ± 14.74	0.03
Male, N (%)	2,265 (59.3%)	2,342 (58.7%)	0.01
Living in Rural area, N (%)	412 (10.8%)	289 (7.2%)	0.12
Myocardial infarction, N (%)	867 (22.7%)	953 (23.9%)	0.03
Electronic record keeping, N (%)	23 (54.8%)	27 (64.3%)	0.20

Covariate constrained randomization



Randomly selected 1000 for our analyses

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Criteria	Randomization method	
	Unconstrained / Simple	Prognostic baseline characteristics
Important prognostic characteristic		
Number of baseline characteristics that were balanced in all 100% of sampled allocations	0%	18%
Number of baseline characteristics that were balanced in at least 95% of sampled allocations	55%	91%

Advantages of CCR

Improved covariate balance: more comparable treatment groups

Reduction in confounding bias: more accurate treatment effect estimates

Enhanced statistical power: increased ability to detect true effects

Limitations and Challenges of CCR

- Computational complexity: may require more time and resources
- Infeasibility: not suitable for all situations (e.g., very small sample sizes)
- Loss of generalizability: careful selection of covariates and balance criteria is crucial

Conclusion

- Recap: covariate constrained randomization is a powerful tool for improving balance in cluster randomized trials
- Encouragement: consult with a statistician ASAP if you are planning to use covariate constrained randomization

A more statistical discussion

- Dr. Fan Li discussing "Linking Design to Analysis of Cluster Randomized Trials: Covariate Balancing Strategies"

https://rb.gy/oirup8

Questions and comments are welcomed

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Thank you

Covariate Balance Metrics

- Assess the quality of balance achieved by CCR
- Examples: standardized mean differences, variance ratios, absolute mean differences
- Compare balance metrics before and after CCR to evaluate improvement