Revisiting Baseline Covariate Adjustment in Randomization and Analysis of Dichotomized Outcome

Yuko Y. Palesch, PhD, Wenle Zhao, PhD, and Yanqiu Weng, DDS, PhD
Data Coordination Unit
Department of Public Health Sciences
Medical University of South Carolina (MUSC)

34th Annual Meeting of the Society for Clinical Trials, Boston, May 19-22, 2013

Covariate Adjustment Issues

- Statistical characteristics
  - Randomization performance criteria (randomness and balance)
  - Operating characteristics (errors, bias in estimates, precision, and efficiency)
- Implementation
  - Complexity in the programming of randomization
  - Correction for mis-execution/errors in randomization
  - Missing covariate data
- Clinical interpretation
  - Concerns about covariate imbalance between groups at the end
  - How to interpret analysis results

Methods Overview

- Created bootstrapped data from a real large stroke clinical trial[1] with two groups and a dichotomized outcome (good vs bad functional outcome).
- Assessed the randomization performance and OC of 3 randomization methods:
  - Simple (SR)
  - Stratified permuted block (SPB)
  - Minimally sufficient balance (MSB)[2]
- Assessed the OC of two analysis approaches:
  - Without covariate adjustment
  - With covariate adjustment with 3 prognostically strong vars: age, disease severity (baseline NIHSS), and time from sx onset to trt.

[1] NINDS rt-PA Stroke Study Group. *N Engl J Med* 1995; 333:1581-1588.
[2] Zhao et al. *Statistical Methods Med Res* pub online 2012 Jan26.

MSB Example

After the first XX subjects who were randomized using SR:

	Mean (sd)		
	Age (in yrs)	Baseline NIHSS	Time to trt (in min)
Tx A	67.96 (11.33)	14.36 (7.46)	119.45 (37.38)
Tx B	65.92 (11.92)	15.21 (6.82)	119.95 (35.98)
t-statistic	2.1898	-1.4784	-0.1685
T-statistic >1.0 or < -1.0?*	Yes	Yes	No
Current patient's covariate values	80	16	99
If t< -1.0, is x > Tx B mean, or if t> 1.0 is x< Tx B mean?	No	Yes	NA
Vote for Tx:	B	A	Neutral

Finally, count up the # of "A" and "B" votes. Assign the current patient with >0.5 probability to the group with greater # of votes. If even, apply SR.

Purpose of MSB is not to achieve exact balance in the covariates but to prevent noticeable imbalances without deterministic assignment.

* Basically assessing whether there is a noticeable imbalance. Intent here is NOT to test for equality of covariates between the treatment groups.

Simulation

- Created pseudo-data via bootstrapping technique with 10,000 simulations for each of the 7 scenarios.

Randomization / Analysis	SR	MSB	SPB (continuous)	SPB (dichotomized)
Unadjusted	X	X	X	
Adjusted for 3 covariates	X	X	X	X

- Simulated for 2 samples sizes: 100 and 400.

Simulation

- Used the logistic regression model for the outcome of dichotomized modified Rankin Scale score (0-1 vs 2-6).
- Assumed H_0:β_{trt}=0 and H_A:β_{trt}=0.8 (OR=2.2) and α=0.05.
- N≈400 for power of ~80% in unadjusted case, given that strong covariate effect exists.
- For SPB, applied a block size of 4, and created 8 strata, 2 for each of the 3 covariates.
- For adjusted analysis, used continuous covariates in its original scale, as well as dichotomized version for the SPB based on the randomization stratification.
- For MSB, used t-statistic with the cutoff of 1.0; and used the biased coin probability of 0.8.

Results

Performance of randomization methods

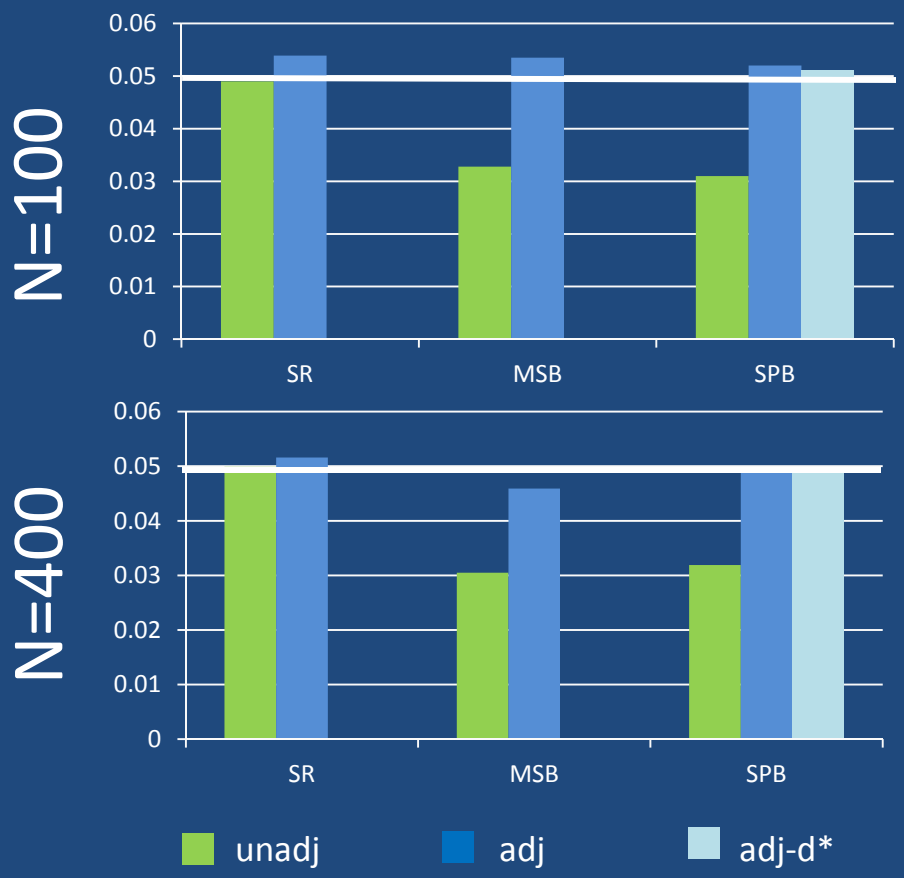
(only for N=400)

	SR	MSB	SPB
Prob. deterministic assignment	0	0	0.325
Prob. of significant imbalance in Age	0.0495	0	0.0017
Prob. of significant imbalance in NIHSS	0.0482	0	0.0005
Prob. of significant imbalance in time	0.0506	0	0
Mean abs. TRT imbalance	15.902	15.904	1.934
SD TRT imbalance	19.924	19.817	2.562

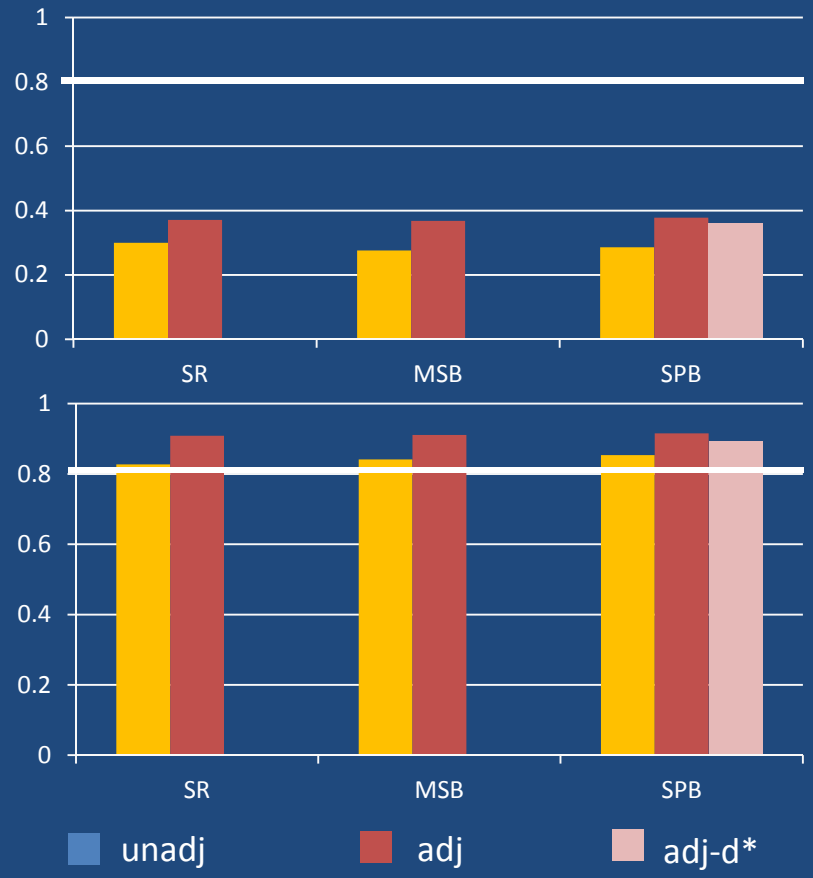
There is a tradeoff between SR/MSB (more random) and SPB (better TRT balance).

MSB is better than SR in balancing of the covariates.

Type I Error



Power



Unadj SPB and MSB are more conservative with any N.

- For a given N, adj analysis yields more power regardless of randomization method.
- Dichotomized covariate analysis is less powerful than continuous.

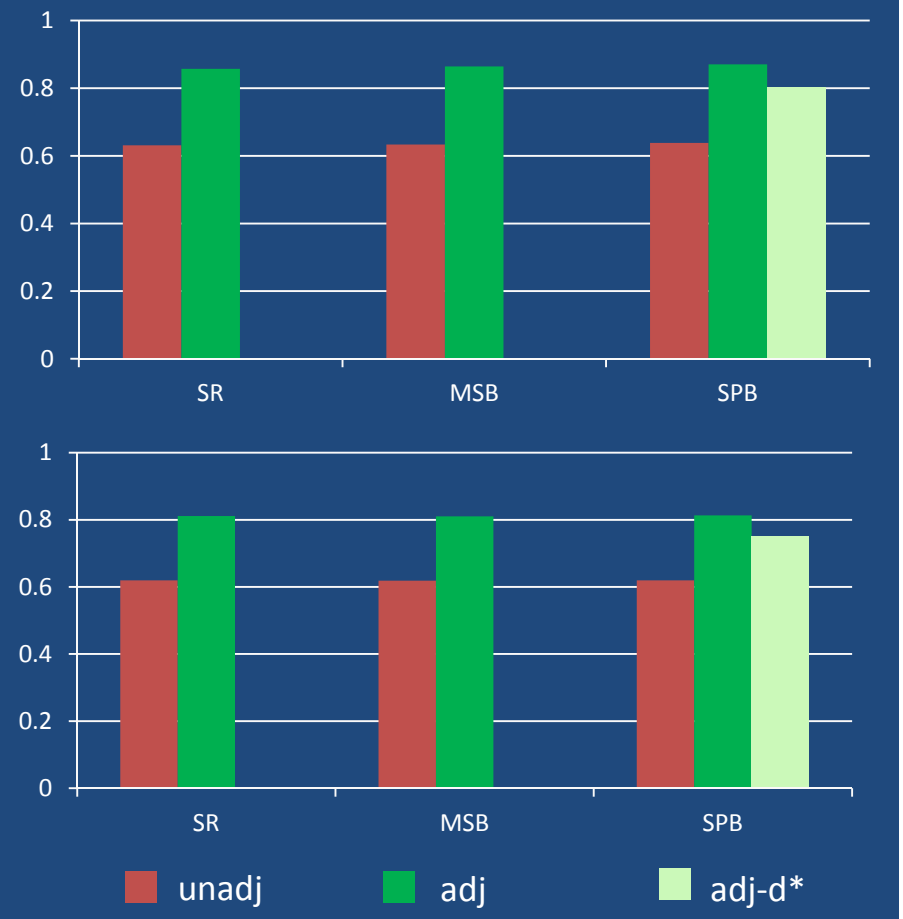
* Adjusted with dichotomized covariates

Trt Est under H_0

Trt Est under H_A

N=100

N=400

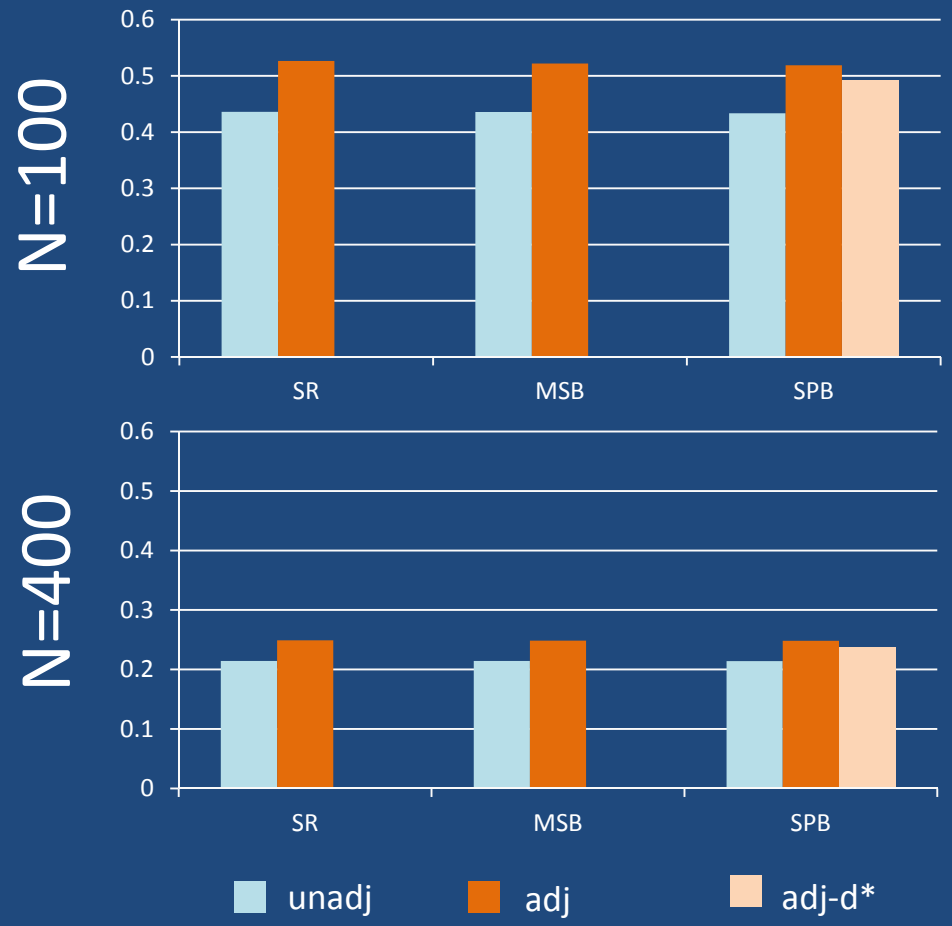


When underpowered, both adj and unadj estimator are biased although in small magnitude.

- Little differences among the randomization methods.
- For adj analyses, slight bias in N=100.
- But unadj analyses yield greatly biased estimates.

* Adjusted with dichotomized covariates

SD Est under H_A



Z Statistic

It is well-known that unadjusted analysis will lead to loss of precision in linear regression. However, this is not necessarily true in logistic regression (Robinson and Jewell, 1991), as confirmed by our results here.

But the adjustments yield more efficient test statistics, regardless of sample size or randomization method.

* Adjusted with dichotomized covariates

Conclusions

- Need to adjust for covariates in the analysis, regardless of the randomization method.
- SR with adjusted analysis may be the best approach statistically and for simplicity in implementation, with the caveat that it may be more vulnerable to challenges to trial result interpretations due to possible covariate imbalances.
- MSB may alleviate that concern while maintaining similar performance levels and OCs.
- Avoid dichotomizing of continuous covariates – still better than not adjusting but is less optimal than using continuous covariates.

The End

Acknowledgement

NINDS funding: U01 NS054630, U01 NS077304, U01 NS061861, and U01 NS 059041