

# Is There Really Any Benefit to Stratified Randomisation Compared to Simple Randomisation with Covariate Adjustment?

**Pavankumar Bhagat | 17NOV2025|PHUSE EU Connect 2025 [AS08]**

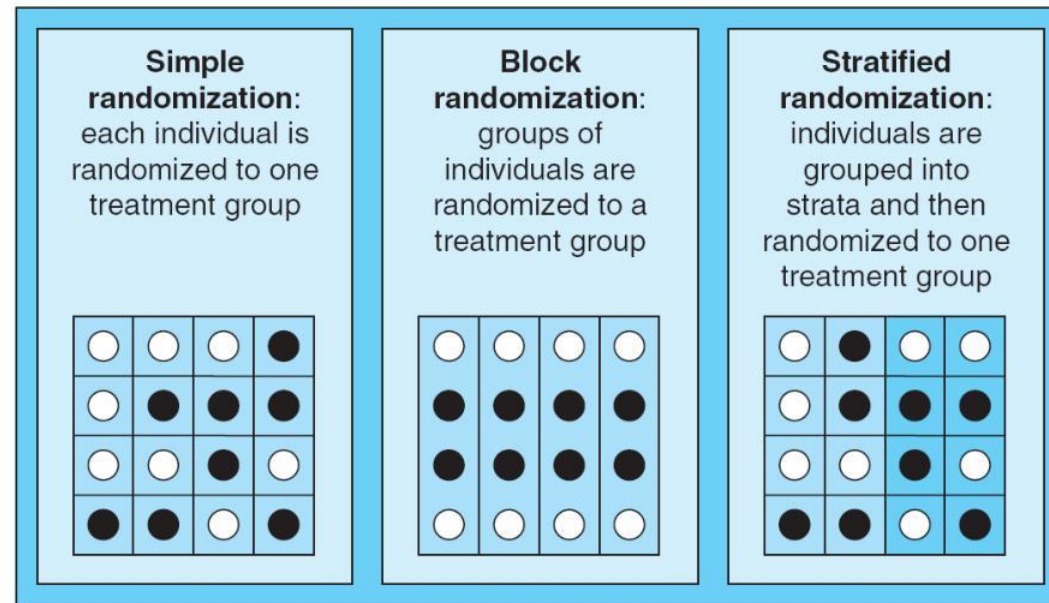
# Disclaimer

- The following slides include statements and approaches that represent my personal perspective and may not necessarily reflect the official positions or recommendations of Boehringer Ingelheim.
- It is important to acknowledge that the subject matter allows for a variety of valid approaches, and the methods I present are not intended to be extensive.
- Where applicable, I have indicated the locations of official sources. The primary focus of this presentation, however, is a description of my past and current research.

- RCTs stands as gold standard in modern clinical trial design[1]
- Reduces selection and assignment bias
- Improves internal validity
- Stratified randomisation reduces random imbalance between treatment groups
- it's unlikely to find imbalances in clinical factors for a randomized large group
- Is stratified randomisation better than simple practically?

# Motivation

## Examples of Types of Randomization



▶ (Jacobsen, 2012, figure 13-6)

# Simulation Study - Continuous outcome

# Simulation study – ADEMP Structure

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Power benefit while  
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## **Performance Measures:**

Power, empirical  
standard error, type I  
error rate, bias, and  
coverage.

# Simulation study – Design and Assumptions

- Design overview: Two-arm, parallel design RCT
- Treatment variable (X1) was generated randomly from a uniform distribution
- Baseline variable (B1) randomly generated from a normal distribution with different means
- Stratification factor variable(B\_stratify) generated with 2 levels based on B1 and threshold of 1
- Treatment variable(X2) was generated using block randomisation and strata factor
- Missing Data: assumed to be complete.
- Significance Level ( $\alpha$ ) = 0.05, outcome variable (Y1/Y2) follows normal distribution.

# Simulation inputs and execution

Sample Sizes: 50, 100, 250, 500

Strength of association between outcome and covariate: weak:  $\log(1.2)$ , moderate:  $\log(2)$ , strong:  $\log(9)$

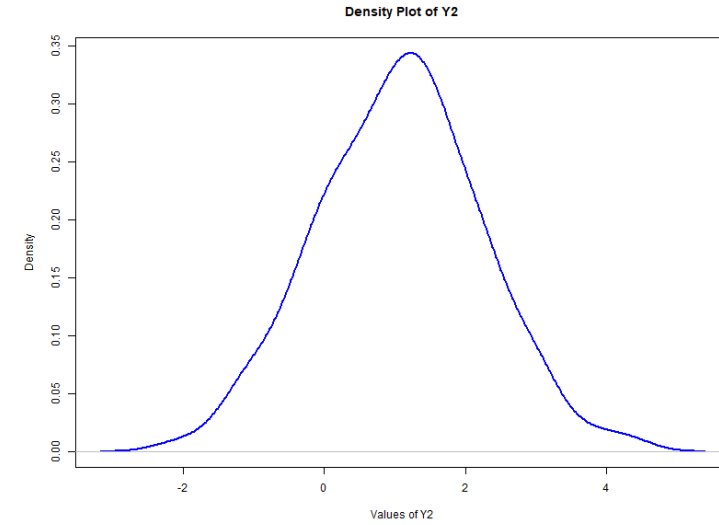
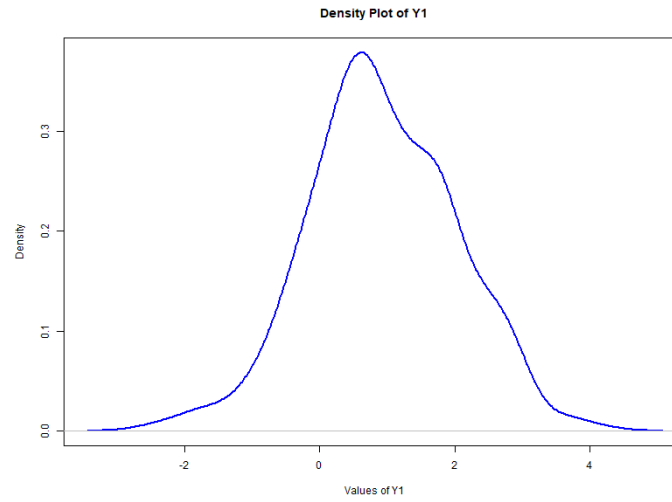
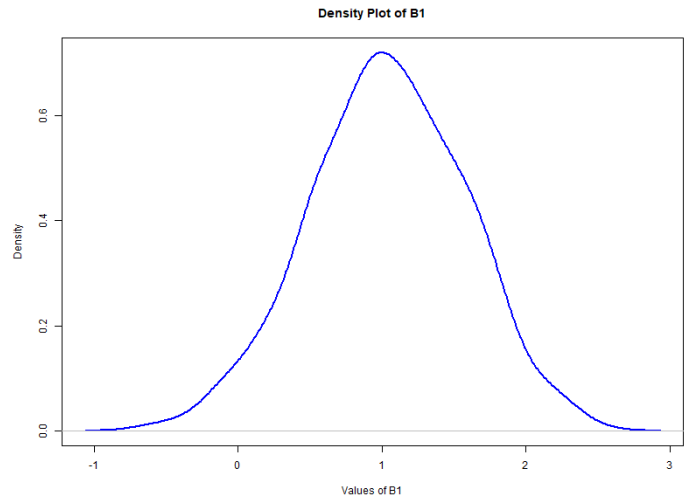
Stratum Proportions: equal ( 50%: 50%) , unequal (80%:20%, 70%:30%)

Iterations: 100,000 simulated datasets.

R-packages: blockrand , dplyr, tidyr , ggplot2

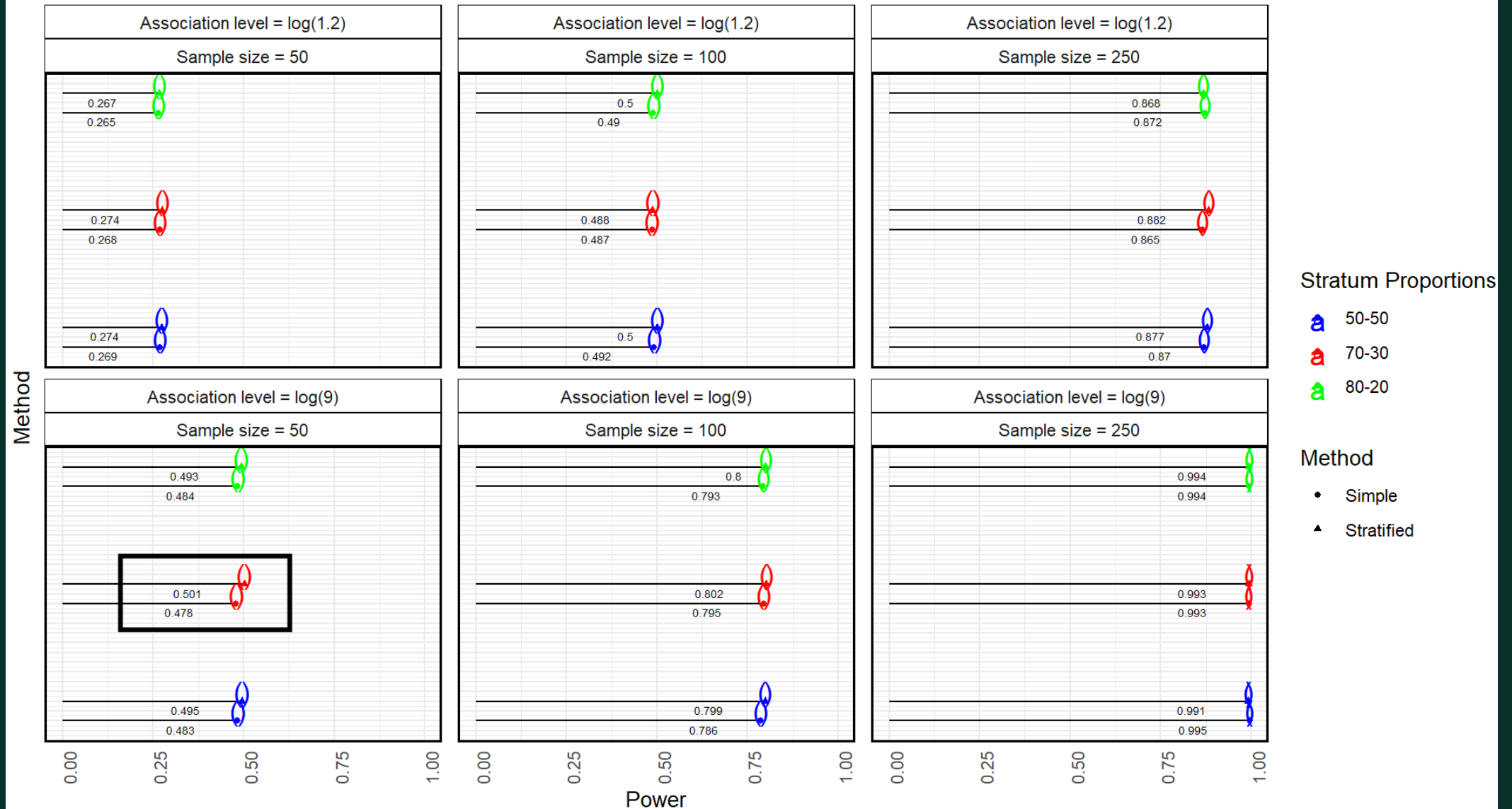
True treatment effect set to 0.6 (for power) , 0 (for Type I error).

# Analysis



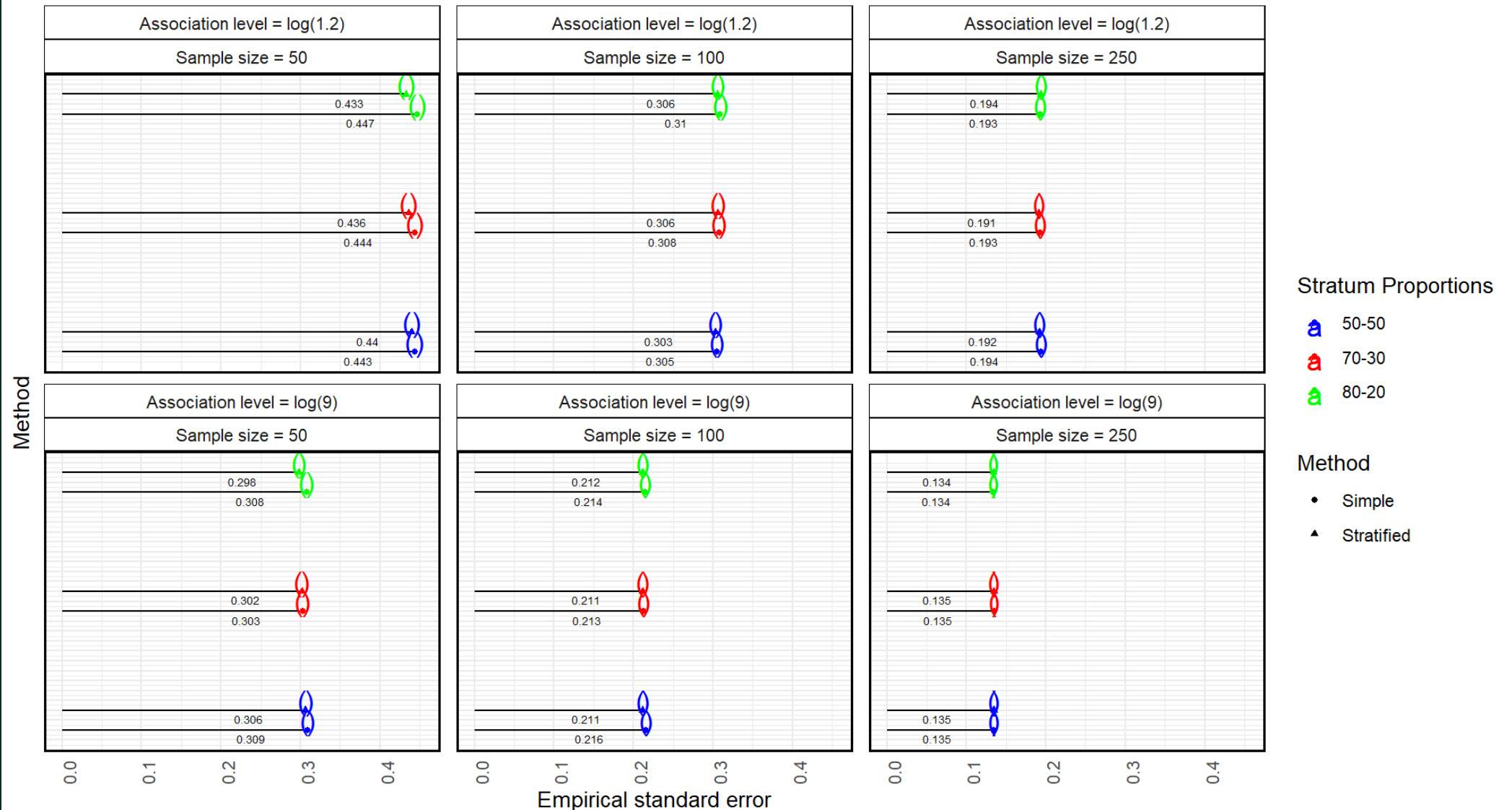
# Results - Power

Power comparison when covariate is adjusted



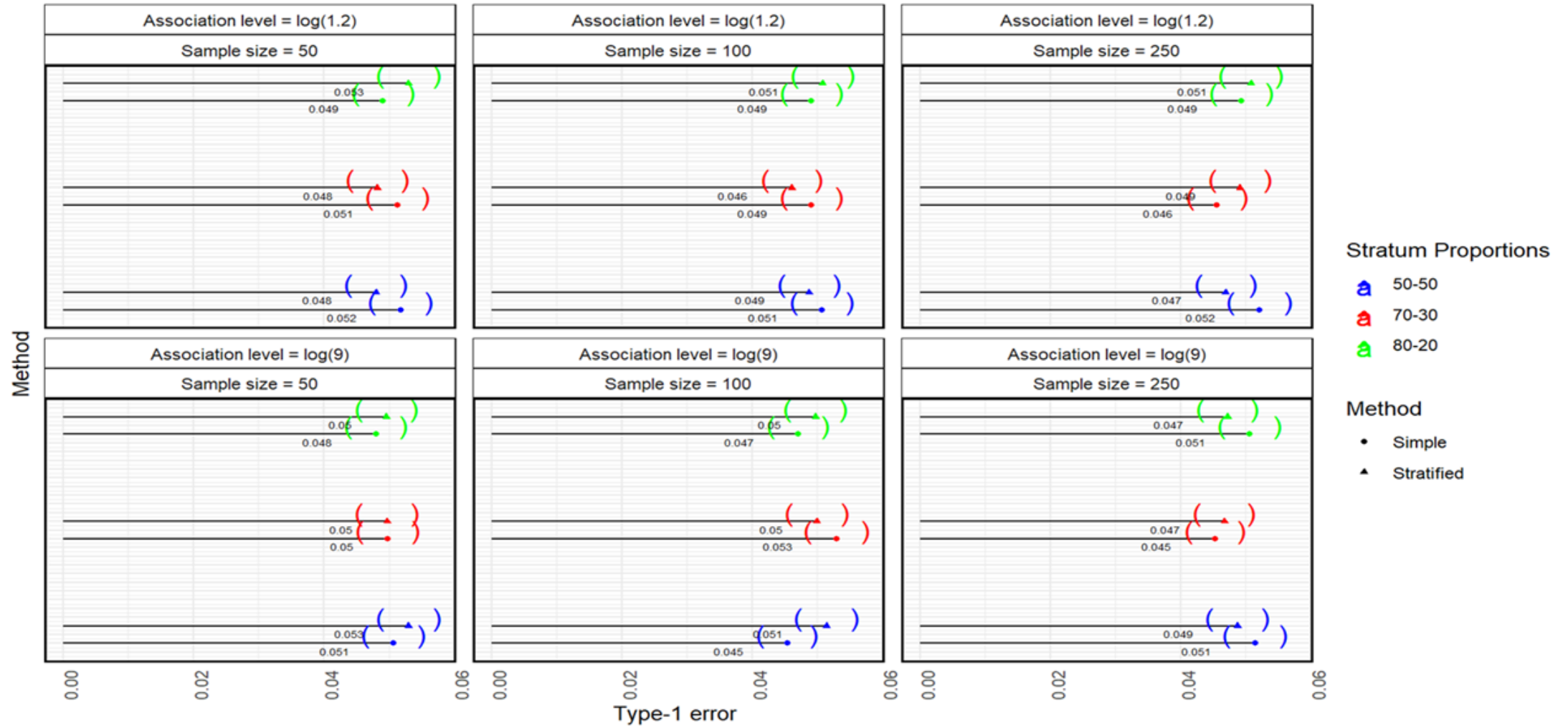
# Results - Empirical standard error

Empirical standard error comparison when covariate is adjusted



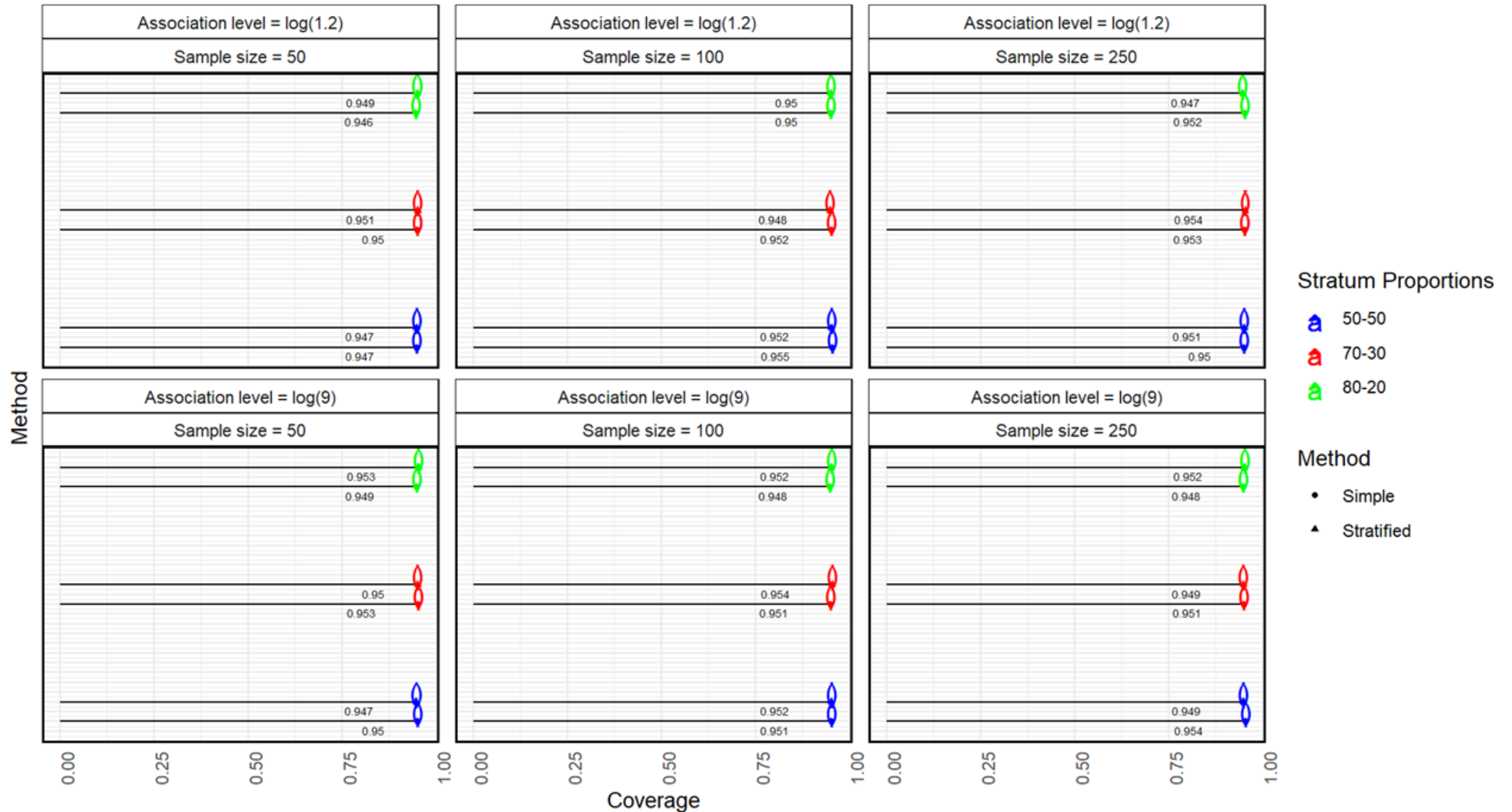
# Results - Type 1- error

Type-1 error comparison when covariate is adjusted

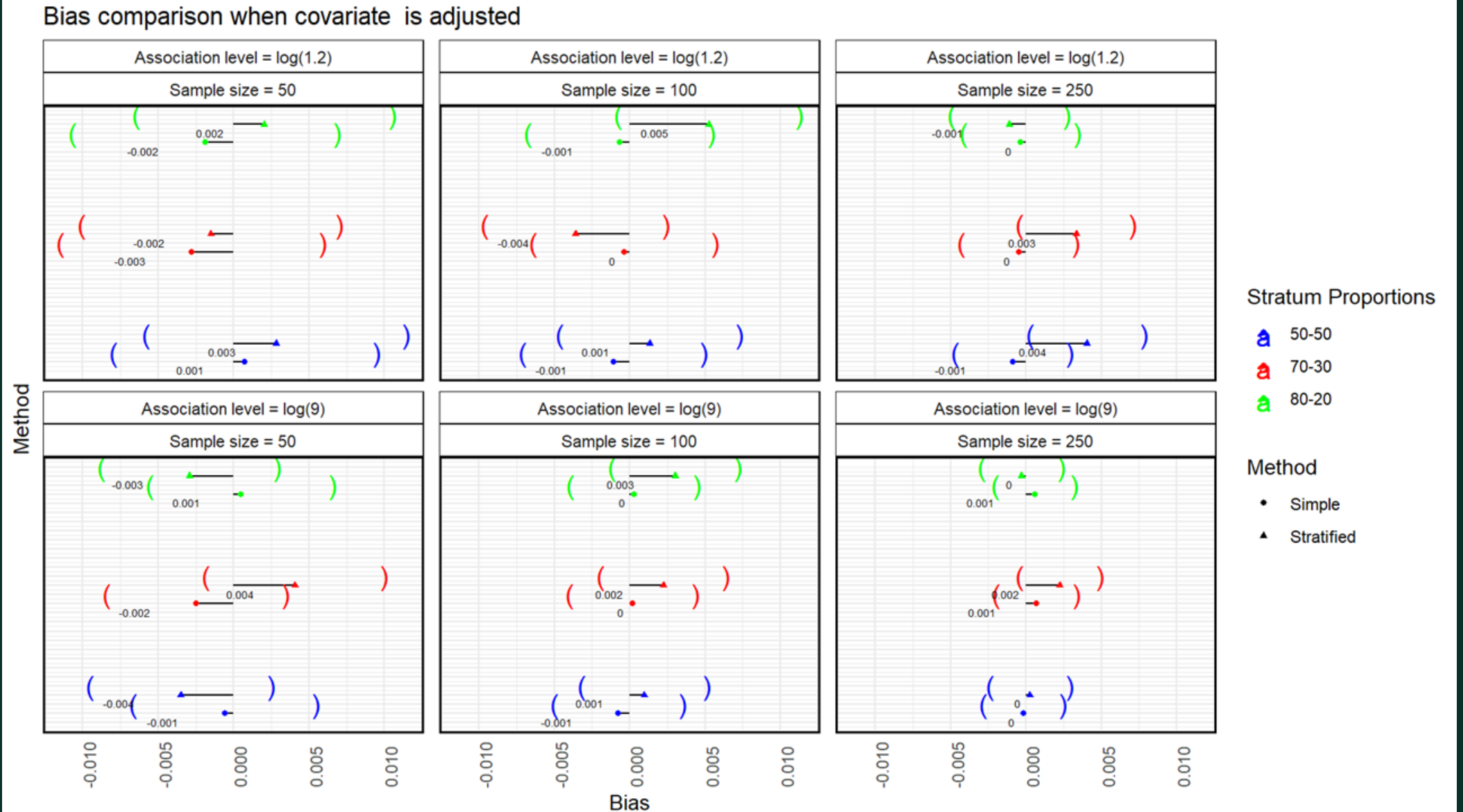


# Results - Coverage

Coverage comparison when covariate is adjusted



# Results - Bias



# Conclusions

## Summary:

- No meaningful benefit of stratified randomisation over simple randomisation with covariate adjustment - especially in large trials.
- Stratified randomisation demonstrates theoretical advantages in balance; however, the complexity may not translate to improved performance in all settings.

## Future Directions:

- Exploration of benefits with different outcomes( binary/time to event )

# Recommendations while using stratified randomization

If we stratify any factors during randomisation, adjust for those during the analysis.

FDA: Pre-specifying co-variate adjustment procedures, especially focusing on prognostic covariates. [\[2\]](#)

How many strata factors we should use? : number should be less than  $n/(B*4)$  [\[3\]](#)

If the strata factors are more ( 4/ 6) it could decrease the power when compared to strata factors with (1/2 ) [\[4\]](#)

if the **baseline covariate** is used to stratify, then we should adjust **actual baseline covariate and not the stratum assignment of the baseline variable** [\[5\]](#)

# Acknowledgements and References

Special thanks to my supervisor from University of Manchester “Dr. Jack Wilkinson” for guidance and supervision during this simulation study.

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- 2. O. of Biostatistics in the Center for Drug Evaluation, R. in cooperation with the Center for Biologics Evaluation, R. at the Food, and D. Administration., “Adjusting for covariates in randomized Clinical trials for drugs and biological products guidance for industry,” Food and Drug Administration, 2023.
- 3. Kernan, W. N. et al. (1999). Stratified randomization for clinical trials.
- 4. B. F. e. a. Anna Moseley, “How many stratification factors are reasonable and can there be too many? evaluation of analysis strategies in the context of a randomized phase 2 trial in acute myeloid leukemia within the myelomatch platform,” ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL, vol. 140, no. 1, pp. 98–108, 2022 .
- 5. European Agency for the Evaluation of Medicinal Products (EMA). Committee for Proprietary Medicinal Products (CPMP): points to consider on adjustment for baseline covariates (London. 22 May 2003. CPMP/EWP/2863/99)

Thank You for your attention 😊