Evaluating the Impact of Strong Covariate Imbalance on Population Adjusted Indirect Treatment Comparisons: A Simulation Study

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Background

Simulated treatment comparisons (STC) and matching adjusted indirect comparisons (MAIC) play an essential role in supporting health technology assessment submissions by facilitating population-adjusted indirect treatment comparisons. In the absence of head-to-head trials, indirect treatment comparisons are required to assess the comparative efficacy of treatments. However, differences in patient-level characteristics may confound unadjusted comparisons. While MAIC and STC can adjust for differences in baseline characteristics, the degree of covariate imbalance observed in the index trial's individual patient-level data may impact the outcome regression model or propensity score model which are constructed as a first step of the adjustment process.

Objective: To evaluate the impact of the degree of covariate imbalance on population-adjusted estimates of treatment efficacy through a simulation study

Methods

The impact of severely imbalanced (between-trials) continuous covariates during an indirect treatment comparison was investigated using population-adjustment methods as follows:

- Patient-level data were simulated using the 'wakefield' package in R (Rinker et al., 2020)
- In the simulation, the following study parameters were applied:
  - Study sample: (n=1000); Note: the sample size was set large enough to allow optimal settings for MAIC as shown in Phillippo et al., 2020
  - Mean age (years) in the index sample was centered at 0 and varied in the comparator sample by increments of +5 (SD=5) years; Note: age was arbitrarily named to represent a continuous variable for ease of communication
  - Prognostic effect of the covariate age (beta coefficient) was set equal to 0.05 units for each 1-unit increase in age
  - Effect modification of age * treatment (beta coefficient) was varied by increments of 0.025 units
  - The absolute treatment effect difference (Δ) was set to -0.4 units
- Each permutation of a 24-dimension Cartesian product of variable age and age effect modification were simulated 1000 times each
- The results of the simulation were summarized using statistical estimates of "bias" and "coverage"
- Bias was estimated as the log-odds of the estimated treatment difference (Δ) minus the true value (-0.4 units) calculated using a naïve comparison, MAIC, and STC each
- Coverage was estimated as whether the 95% confidence intervals for each permutation were contained within the true treatment difference
- Linear regression was used to test the significance of covariate imbalance and effect modification in predicting bias

References

1. Phillippo, D. M., Ades, A. E., Dias, S., Palmer, S., Abrams, K. R., & Welton, N. J. (2016). NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. *Report by the Decision Support Unit*.
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3. Rinker, T., O'Brien, J., Mahto, A., Sigal, M., Carroll, J., & Westenberger, S. (2020). Generate Random Data Sets. Version 0.3.6. *Package 'wakefield'*, 1-98.

Abbreviations: DSU, decision support unit; NICE, National Institute for Health and Care Excellence; MAIC, matching adjusted indirect comparison; STC, simulated treatment comparisons; TSD, technical support documents.

Results

Figure 1. A) Forest plot of bias stratified by between-study covariate imbalance and population-adjustment method, and **B)** bar chart of coverage stratified by between-study covariate imbalance and the population-adjustment method.

- There were no linear trends in increased bias when varying the magnitudes of between-study age imbalance (STC, p=0.731; MAIC, p=0.809) or effect modification strength (STC, p=0.124; MAIC, p=0.293) [linear regression, not shown].
- **Figure 1A** shows that bias remains stable within Naïve, MAIC, and STC when summarized over the increasing age imbalance (Δ=5 – 30).
- The absolute bias in Naïve, MAIC, and STC adjustments, remain small relative to the magnitude of the true treatment value, -0.06/-0.4 (15%), -0.01/-0.4 (3%), and 0.03/-0.4 (8%), respectively. Note: Most extreme value reported.
- MAIC and STC demonstrate improvements relative to the Naïve comparison through reduced bias as expected, given effect modification is present (0 to 8%).
- All three methods demonstrate high coverage (94 to 95%) within each age imbalance (**Figure 1B**).

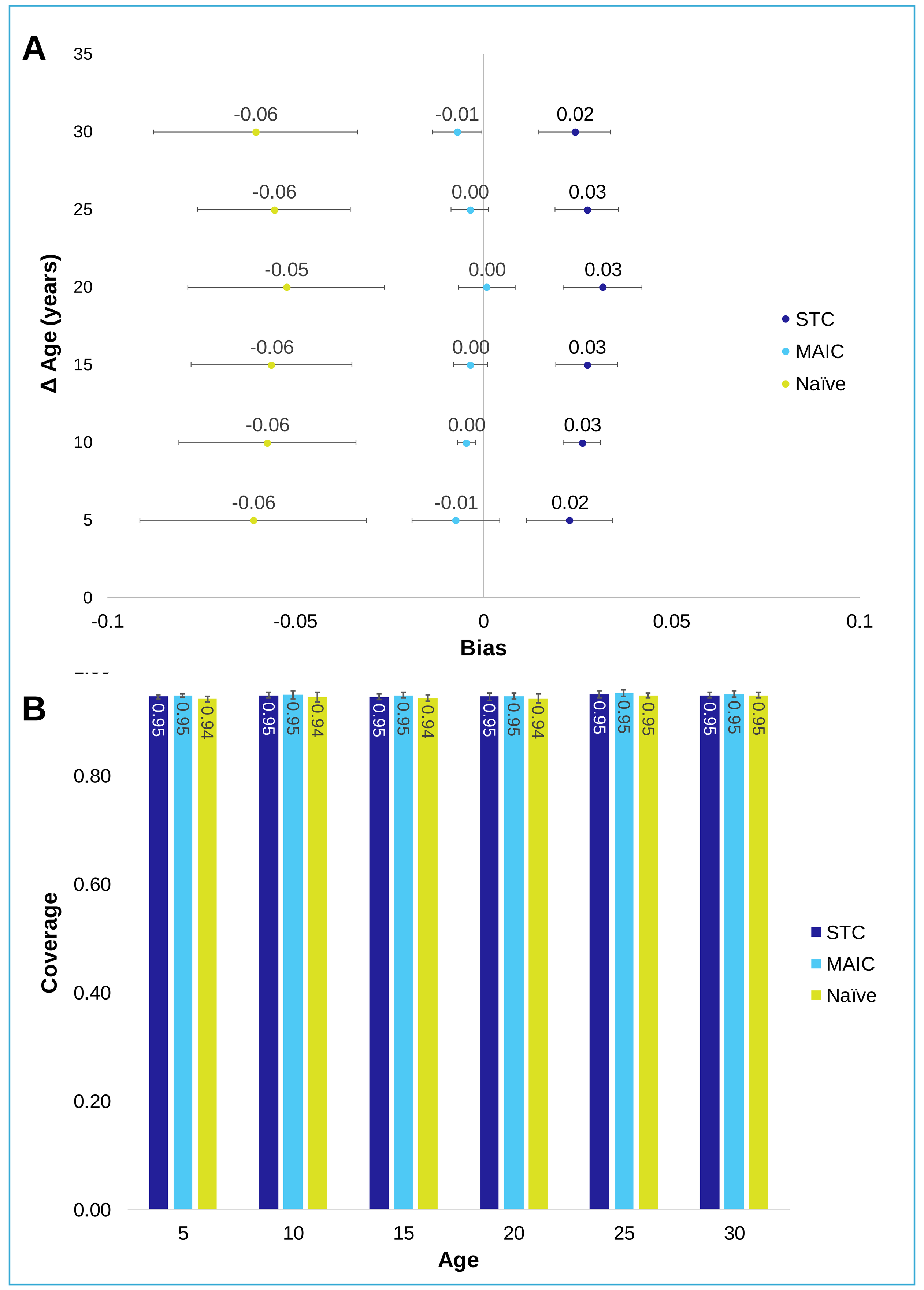
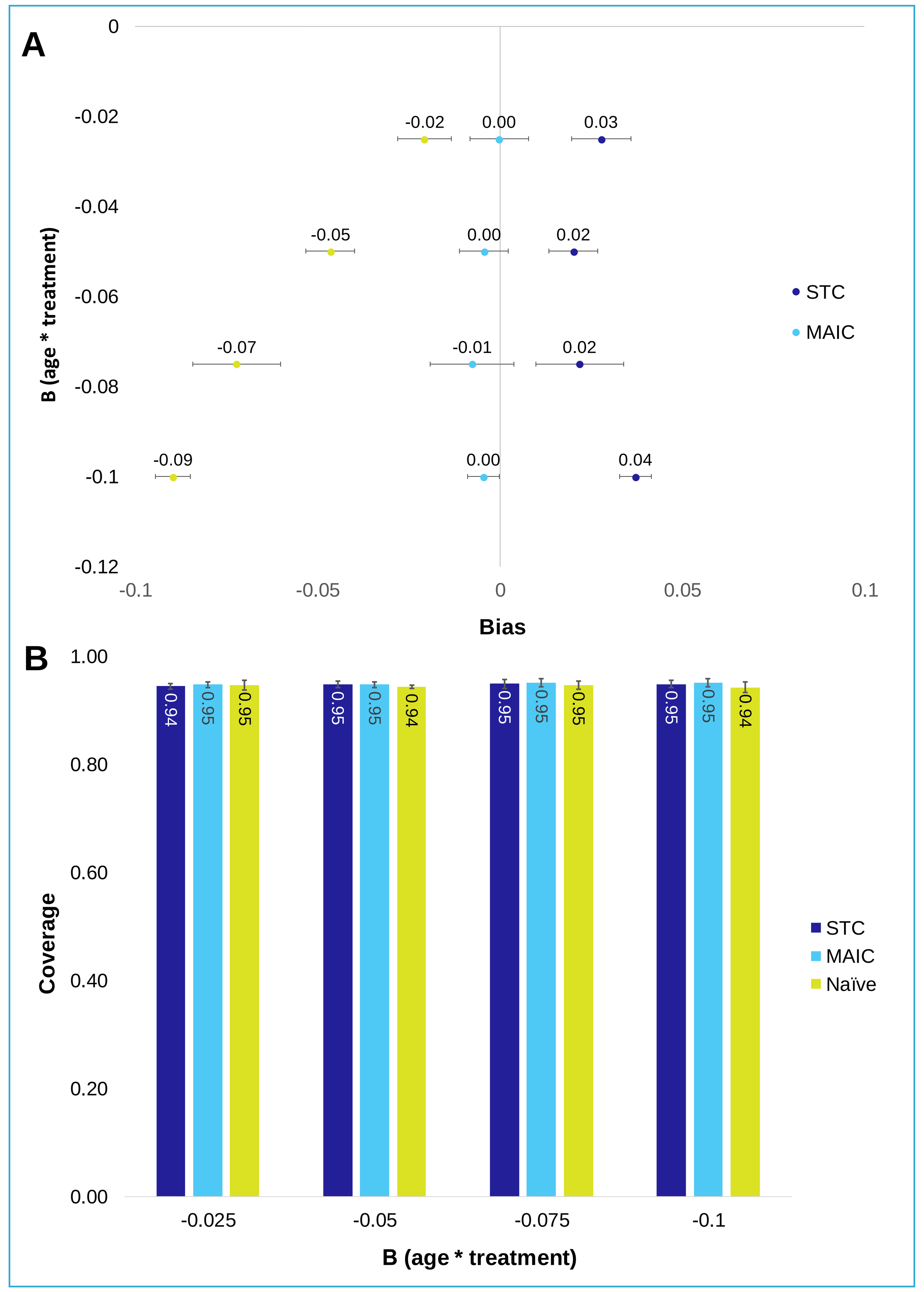


Figure 2. A) Forest plot of bias stratified by effect modification covariate strength and population-adjustment method, and **B)** coverage of bar of coverage stratified by effect modification covariate strength and population-adjustment method.

- A pattern of bias is shown to increase linearly in the naïve comparison when the effect modification strength increases (B = -0.1; MAIC = -0.09) (**Figure 2A**).
- Population-adjustment methods, MAIC and STC, remain unaffected when the effect modification is strengthened (B = -0.1; MAIC = 0.00, STC = 0.04), demonstrating their intended strengths in removing bias when effect modifiers are imbalanced between studies.
- Over the range of effect modification strength tested in this simulation, the bias increased in the naïve comparison by 17.5%.
- All three methods continued to demonstrate high coverage (94%–95%) (**Figure 2B**).
- Overall, the results are in accordance with NICE DSU TSD18 (Phillippo et al., 2016) and affirm that population-adjustment methods (MAIC, STC) are preferrable to the Naïve method when effect modification is present and when there are considerable imbalances between trials.



Limitations

This study was limited in several ways:

- The simulation used only a continuous covariate as an example and assumed it to be linear in effect
- If the underlying effects of covariates are non-linear, these results are no longer expected to hold true
- The parameters in this study represent an arbitrability derived scenario and are hypothesized to be reasonable based on the authors' knowledge of population-adjustment methodology, statistical analysis, and real-world applications
- Twenty-four permutations were applied to reach findings; with an infinitesimal number of ordered combinations possible, the applied scope was limited
- The size of the treatment effect and the standard deviation of mean continuous covariate were not varied; this is not anticipated to change the result of the bias trajectories

Conclusions

- STC and MAIC perform without meaningful bias within plausible ranges of effect modification strength when there are strongly imbalanced covariates between studies.
- Therefore, if the effect modification of a covariate is known to be linear, the degree to which the covariate is imbalanced between trials can be accurately adjusted for using population-adjustment methodology.
- Both STC and MAIC improve upon naïve comparisons with respect to bias when effect modification is present; in the simulation, this was demonstrated through the maintenance of a constant magnitude of bias while the effect modification strength was increased.
- This simulation supports the rationale that bias in indirect comparisons results from improper covariate selection or modelling of the covariates rather than the strength of the imbalance.