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Methods for covariate adjustment in cost-effectiveness analyses of cluster randomised trials.

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Objectivos (Objectives): Cost-effectiveness analyses (CEA) alongside clinical trials are typically conducted on the assumption that randomisation ensures the absence of systematic imbalances in the baseline covariates. However, in cluster randomised trials (CRTs), where the randomisation is by cluster rather than individual, systematic differences in individual and cluster-level covariates between the treatment groups can arise. For example, a general concern with CRTs is that studies tend to be unblinded, with individuals recruited after treatment allocation to clusters is known. Hence, cluster randomisation can encourage systematic imbalances in baseline characteristics, which if associated with outcomes, can lead to systematic bias. This study presents an assessment of the relative performance of alternative analytical methods that adjust for these systematic imbalances in observed covariates in CEA of CRTs.

Metodologia (Methodology): This paper considers three methods: seemingly unrelated regression (SUR) with a robust standard error; a non-parametric 'two-stage' bootstrap (TSB) approach combined with SUR; and multilevel models (MLMs). As a motivating example, we firstly considered the methods in a CEA of a CRT with covariate imbalance and a prognostic relationship that differ by treatment group. We then conducted an extensive simulation study to compare the methods across a wide range of circumstances such as increasing levels of confounding, cluster size variation, few clusters, and prognostic relationships that differ between treatment groups. Performance was reported in terms of bias, variance, root mean square error (rMSE) and confidence interval (CI) coverage of the incremental net-benefit (INB).

Resultados (Results): The results from the case-study showed that cost-effectiveness estimates changed considerably after covariate adjustment, and according to method. In the simulations, we show that failing to adjust for covariate imbalance can lead to biased results, even with low levels of confounding. With covariate adjustment, all methods provided relatively low levels of bias across the scenarios considered. However, the performance of adjusted methods differed in terms of precision and CI coverage. The approach combining the TSB with SUR produced relatively low CI coverage across all scenarios (<0.91, for a nominal level of 0.95). SUR alone reported lower levels of precision (variance and rMSE) and CI coverage than MLMs, particularly in scenarios with few clusters or unequal cluster sizes.

Conclusões (Conclusions): Our study extends current literature examining the relative merits of hierarchical models, robust estimation, and non-parametric bootstrap approaches for covariate adjustment. In a context where methods are required to address systematic differences between treatment groups as well as accommodating clustering and correlation between costs and health outcomes, we find that MLMs are the most appropriate method across a wide range of circumstances. The methods considered here assume no confounding on unobservable covariates (hidden bias), for which other methods such as instrumental variables estimation may be required. We encourage future CEA of CRTs to consider imbalance in potential confounders in pre-specified analysis plans to help studies provide a sound basis for policy-making.