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ABSTRACT TEMPLATE

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Covariate Balance Assessment in Propensity Score Matching After Multiple Imputation With Chained Equations: An Empirical Example

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Background: Multiple imputation with chained equations (MICE) is a popular approach in observational studies to account for missing values in covariates. Although different approaches of applying propensity score matching (PSM) after MICE have been proposed, the impact of each approach on covariate balance has not been evaluated.

Objectives: To assess the impact of different PSM-MICE approaches on covariate balance and treatment effect estimate.

Methods: We used the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) to study the association between oral bisphosphonates (OBP) and the risk of acute kidney injury (AKI). We applied PSM after MICE and assessed covariate balance using absolute standardized mean difference (ASMD) in three ways: (I) Estimate the PS in m imputed datasets, PSM the m imputed datasets, calculate ASMD and estimate treatment effect in each of m datasets and average the m ASMDs and treatment effect estimates using Rubin's rules. (II) Similar to the previous one but PS from m imputed datasets are first averaged. Patients are then PSM using the

average PS, from which the ASMD and treatment effect were estimated in one dataset. (III) Estimate PS using one PS model, average PS for each patient across m datasets, PSM on the average PS, and calculate ASMD and treatment effect on the PSM dataset. We PSM-matched 1:5 with caliper 0.20 standard deviations on the logit of the PS, estimated hazard ratios and 95% confidence intervals (95%CI) using Cox proportional hazard models, and compared covariate balance and HRs from the three approaches.

Results: The three approaches retained similar number of outcome events treated/controls, n = 253/1597, 253/1604, 256/1668 for I, II and III, respectively. They also resulted in similar ASMD and treatment effect estimates, HR[95% CIs]: 0.93 [0.80, 1.07], 0.91 [0.80, 1.04], 0.90 [0.79, 1.03] for approaches I, II and III, respectively. Covariate balance was slightly better with the first approach (I) particularly for covariates with missing values in the original data. Approaches I and II were similar with respect to covariate balance.

Conclusions: In general, the different approaches were similar with respect to covariate balance and treatment effect estimate in our example. This could be due to the confounding structure of the dataset we used, hence, generalisation requires a simulation study. We recommend balance assessment should be conducted in line with treatment effect estimation.