Evaluating effectiveness of case-matching for exposure-response analysis

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Objectives
Accurate characterization of exposure-response (E-R) relationships can be challenging in the presence of confounding factors that affect both pharmacokinetic (PK) properties as well as response. In such situations, virtual randomization using case-matching of treatment arm subjects has been proposed to select control arm subjects for inclusion in the E-R analysis [1]. We present two approaches to evaluate the effectiveness of the virtual randomization by case-matching with respect to PK properties (that are not observable in control arm subjects).

Methods
Case Matching Evaluation
The proposed case-matching evaluation methods are illustrated for a 2-arm clinical trial of drug (treatment) vs placebo (control), in which treatment arm subjects with exposures in the lowest quartile are matched to control arm subjects by propensity score matching. The effectiveness of the matching with respect to exposure is assessed by:

1. Holding out half the subjects in the treatment arm and attempting to match within the treatment arm.
2. Reverse matching the identified control subjects back to the treatment arm, and comparing exposure to what would be expected.

Simulation
The validity of these methods were assessed for several simulated scenarios with varying sample sizes (N_treatment = N_control = N = 100, 200, 500), number of continuous covariates (p = 5, 10, 20), and correlation among covariates and exposure (ρ = 0.0, . . . , 0.99) while taking σ² = 0.25 to be fixed. For each subject we generate the (p + 1) × 1 vector

\[ X_i = [X_{i0} \mid X_{i1} \cdots \mid X_{ip}] \]

consisting of a measure of exposure, X_{i0} and the p covariates, X_{i1}, . . . , X_{ip}, according to

\[ X_1, \ldots, X_{2N} \sim N_{p+1}(μ = 0_{p+1}, Σ = σ^2[(1 - ρ)I_{p+1} + ρ 1_{p+1}1_{p+1}]) \]

such that the pairwise correlation among all the covariates and between each of the covariates with exposure is ρ.

Case Matching
All case-matching was performed using a logistic propensity score model [2] that included all covariates. Matches were selected at random from candidates with propensity scores within a caliper of 0.2 times the standard deviation of the propensity score distribution.

Results
The effectiveness of case-matching improved with increasing correlation among exposure and matched covariates, and with larger sample size. Both evaluation methods were useful for assessing the effectiveness of the case-matching. Specifically, the percentage of matched hold-outs or reverse-matched treated subjects with exposure in the lowest quartile was predictive of the percentage of matched controls expected to have exposure in the lowest quartile. Likewise, the Absolute Standardized Difference in Mean (ASDM) exposure between subjects in the lowest quartile and the matched hold-out subjects (i.e., ASDM = \(|x_{Q1} - \bar{x}_{matched}/σ_{Q1}|\) was predictive of the ASDM for exposure expected with matched controls.

Case-Matching Quality vs. Covariate-Exposure Correlation

References