Evaluating effectiveness of case-matching for exposure-response analysis

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Objectives

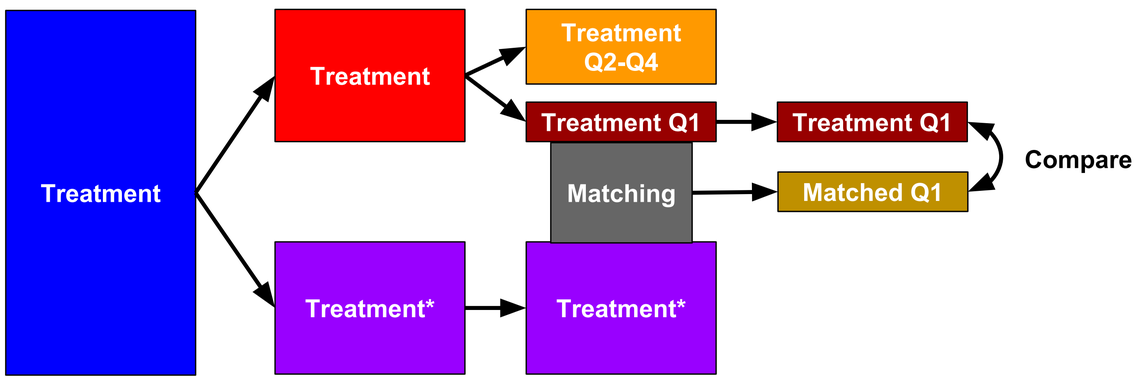
Accurate characterization of exposure-response (E-R) relationships can be challenging in the presence of confounding factors that affect both pharmacokinetic (PK) properties as well as response. In such situations, virtual randomization using case-matching of treatment arm subjects has been proposed 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

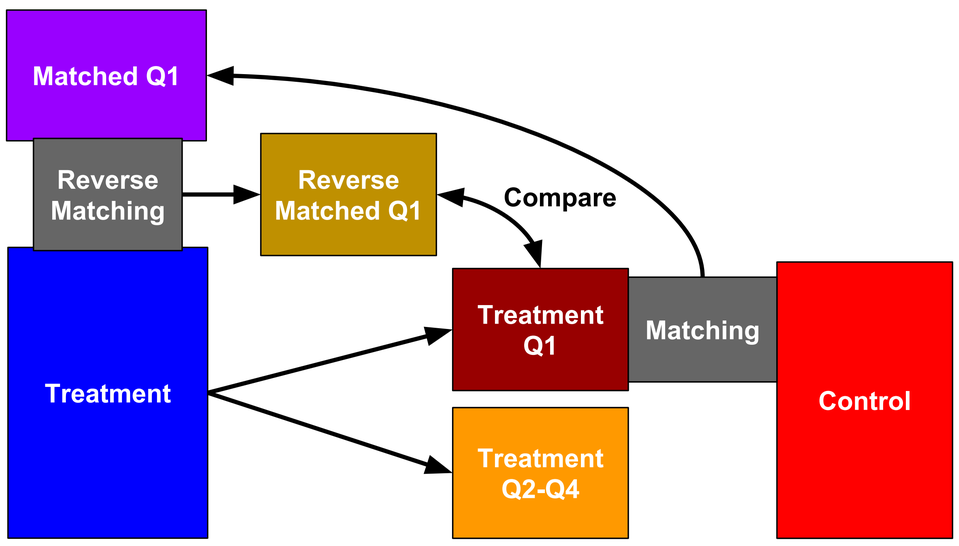
Case Matching Evaluation

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 ($N_{trt} = N_{ctl} = N = 100, 200, 500$), number of continuous covariates ($p = 5, 10, 20$), and correlation among covariates and exposure ($\rho = 0.0, \ldots, 0.99$) while taking $\sigma^2 = 0.25$ to be fixed. For each subject we generate the $(p+1) \times 1$ vector

$$\boldsymbol{X}_i = \left[\; X_{i0} \; \middle| \; X_{i1} \quad \cdots \quad X_{ip} \; \right]$$

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

$$\boldsymbol{X}_1, \ldots, \boldsymbol{X}_{2N} \sim N_{p+1}\left(\boldsymbol{\mu}=\mathbf{0}_{p+1}, \boldsymbol{\Sigma} = \sigma^2\left[(1-\rho)\boldsymbol{I}_{p+1} + \rho\,\mathbf{1}_{p+1}\mathbf{1}'_{p+1}\right]\right)$$

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.

References

[1] Yang, J., Zhao, H., Garnett, C., Rahman, A., Gobburu, J.V., Pierce, W., Schechter, G., Summers, J., Keegan, P., Booth, B. and Wang, Y. The combination of exposure-response and case-control analyses in regulatory decision making. *J Clin Pharmacol* **53** (2013):160–6.

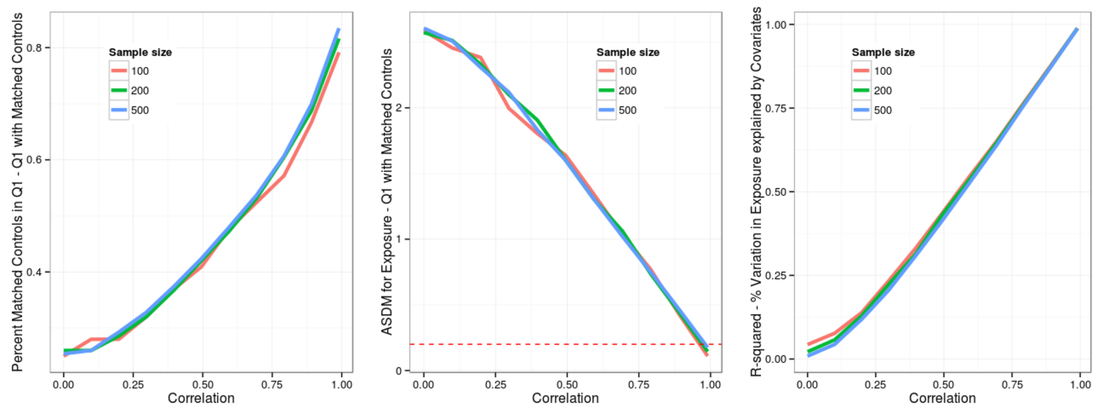
[2] D'Agostino, Jr, R.B. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* **17** (1998):2265–81.

Results

The effectiveness of case-matching improved with increasing correlation among exposure and matched covariates, and with larger sample size.

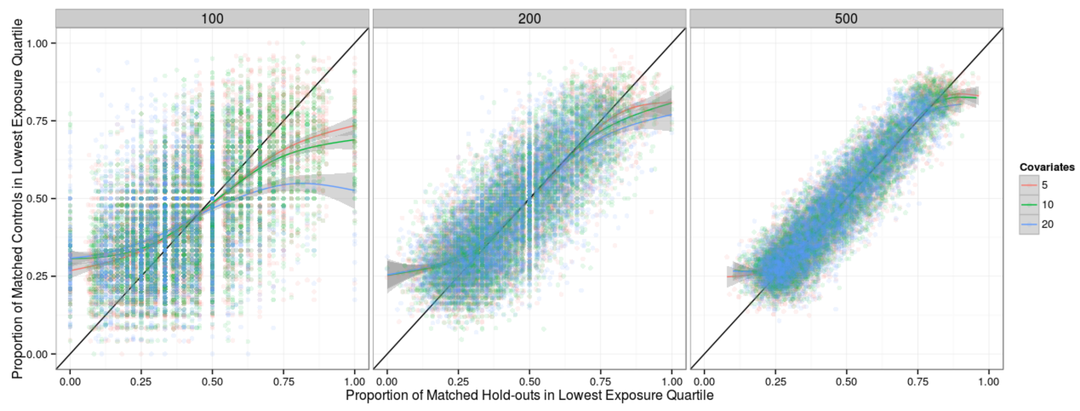
Both evaluation methods were useful for assessing the effectiveness of the case-matching. Specifically, the percentage of matched hold-outs or reverse-matched treated subjects with exposure in the lowest quartile was predictive of the percentage of matched controls expected to have exposure in the lowest 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=$|\bar{x}_{Q_1} - \bar{x}_{Matched}|/s_{Q_1}$) was predictive of the ASDM for exposure expected with matched controls.

Case-Matching Quality vs. Covariate-Exposure Correlation



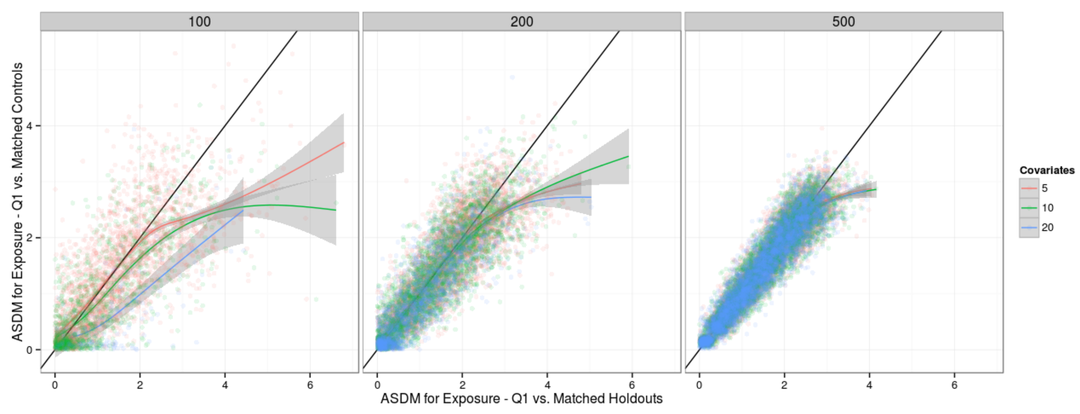
Performance of Hold-out Evaluation Method (% Low Exposure)

Smooth functions with shaded regions represent generalized additive models with 95% confidence bands



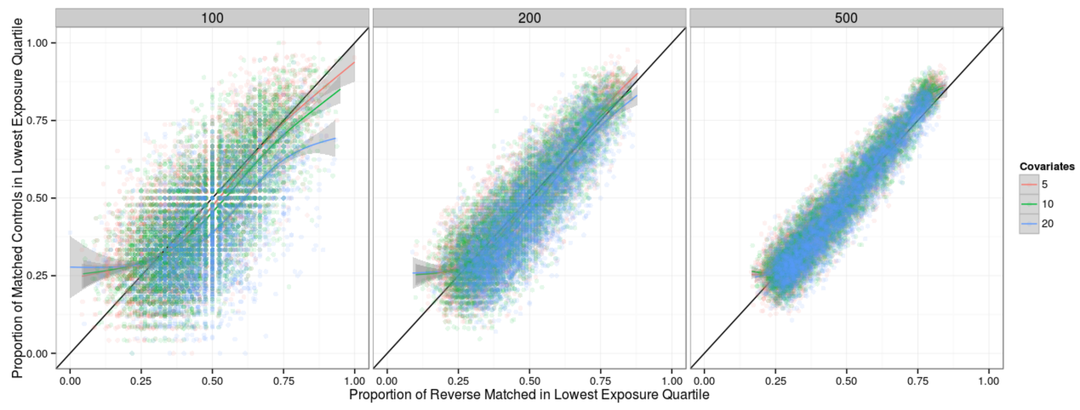
Performance of Hold-out Evaluation Method (ASDM for Exposure)

Smooth functions with shaded regions represent generalized additive models with 95% confidence bands



Performance of Reverse-Matching Evaluation Method (% Low Exposure)

Smooth functions with shaded regions represent generalized additive models with 95% confidence bands



Conclusion

- The "Hold out" method and the "Reverse matching" method were both shown to be a useful part of a case-matching evaluation strategy in the context of exposure-response analysis
- In the context of exposure-response analysis, case-matching is increasingly used to identify a subset of the control arm with a similar covariate distribution to those of the subset of the treatment arm with low-exposure. However, the probability that the matched controls would have similarly low exposure (were they to be treated) is dependent on the correlation between the measured covariates and exposure.
- It is recommended that effectiveness of case-matching is evaluated prior to performing exposure-response analysis on non-randomized subjects, to ensure that the matching results in balanced distributions of observed and unobserved factors that may affect both exposure and response.