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STUDENT CORNER

Analytical Approaches to Achieve Quasi-Randomization in Retrospective Database Analysis

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Perhaps randomization is one of the characteristics that granted controlled, clinical trials (RCTs) the "gold standard" label for causal inference of exposure effect. By randomly assigning patients to exposure groups, randomization is the only approach that ensures an equal—or nearly equal—distribution of measured and unmeasured confounders across exposure groups. Lack of randomization in observational epidemiological designs—including retrospective database studies—predisposes them to a myriad of limitations that affect the interpretation of findings from such studies [1]. Considering the ethical and logistical weaknesses of RCTs, well designed and conducted observational studies are efficient in exploring exposure safety and effectiveness. Although comparability across exposure groups is rarely guaranteed in observational studies, multiple analytical approaches are utilized to achieve a "quasi-randomization" state [2], which results in unbiased estimates of association between the exposure and the outcome of interest. Propensity scoring, instrumental variable, and disease severity measures are some of these approaches (Table 1).

Propensity Scoring (PS)

Propensity scoring adjusts for the likelihood of a patient being exposed given a set of measured confounders [3]. This method is mainly used to account for selection bias and confounding by indication. Although PS balances confounders across exposure groups, it does not balance unmeasured confounders [4]. Propensity score is defined as the probability of receiving an exposure given baseline information (i.e. confounders). On average, groups with similar scores are expected to have similar baseline information. There are four applications of the PS technique:

- *Propensity Score Matching:* Patients can ostensibly be treated as if they were randomly assigned to exposures by matching exposure groups with similar scores based upon a PS scalar/caliber. One limitation of this approach is restricting generalizability of exposure effect to a subset of patients with overlapping scores across groups [5].

- *Propensity Score Stratification:* Exposure groups can be grouped into strata based on the score, where a stratum-specific treatment effect can be estimated [6]. Both applications can be used to evaluate the comparability of exposure groups by checking for overlap across scores. Residual confounding, however, could occur as a result of score categorization [7].

- *Propensity Score Regression:* Incorporating the score as a covariate in the regression model will simplify the final model in terms of the number of covariates [6]. Compared to the earlier two methods, the effect of some important covariates on the outcome can be elucidated in regression models. Model misspecification, however, can be a limitation in this method [7].

- *Inverse Probability of Exposure Weighting (IPW):* The inverse of the propensity score can be used to create a weighted average of the exposure effect. IPW is defined as the inverse of the probability of receiving the exposure actually received [8]. Compared to the PS matching technique, the IPTW uses the whole sample data for analysis, which enhances generalizability. Additionally, IPW extends to multicategory exposure groups, and time-varying exposures [7]. Weight instability, however, occurs when some exposure groups become uncommon [4,7].

Instrumental Variable (IV)

As mentioned above, PS methods do not account for unmeasured variables. In case of unavailability of an important confounding factor, using a variable, denoted an instrument can account for this problem. Three conditions, however, ought to be met in a variable in order to be an IV (Fig. 1) [9]. The variable (I):

1. Is associated with exposure (E). Either (I) causes (E) (solid gray arrow), or both share a common cause (C).

Figure 1. Characteristics of an instrumental variable

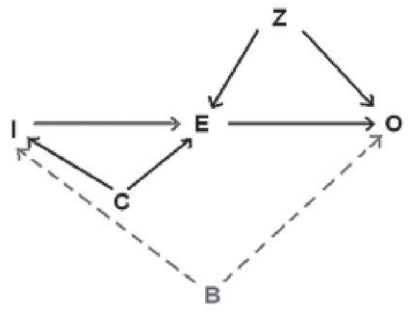

Table 1. Problems that can be controlled by different analytical approaches

Approach	Problem
Propensity Scoring.	• Selection Bias. • Confounding by Indication: ▪ Confounding by Disease Severity. ▪ Channeling Bias.
Instrumental Variable.	• Selection Bias. • Residual Confounding. • Unmeasured Confounding.
Disease Severity Measures.	• Selection Bias. • Confounding by Indication: ▪ Confounding by Disease Severity. • Residual Confounding.

2. Affects the outcome (O) only through the exposure (I – E – O).

3. Doesn't share a common cause (B) with the outcome (dashed gray arrows).

Although this approach is imperative in accounting for unmeasured confounders and minimizing residual confounding, it is very difficult to identify and measure a good IV that meets the above-mentioned conditions and fits the research question in hand.

Disease Severity Measures

When patients with high disease severity are preferentially prescribed specific medications, confounding by disease severity is said to occur [2]. This problem can be accounted for by identifying proxy variables that implicitly depict the disease state, and include them in the covariate pool of the PS technique. The disadvantage of this approach goes in tandem with the limitation of the PS mentioned above (i.e. failure to adjust for unmeasured severity-related variables). Yet, using rich databases will account for much of these measures.

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