Methodological Considerations

The strength of IV can be determined by how closely associated the instruments are with the exposure experienced by the patient. In some types of randomization, this might lead to an absolute correspondence (like with a vaccine). In other forms, the association is diluted by adherence to medicinal products, becoming weaker as the level of adherence drops. The need to have the strongest possible instrument is one of the justifications for trying to optimize adherence in RCT. With a strong instrument, it is possible to analyze the instrument directly, as a proxy for the exposure. In RCT, this is known as ITT and will generally create a conservative bias in estimation.

However, the types of variables that are considered in noninterventional PASS are weak instruments. Generally, randomization is not called an instrument in studies of drug effects but forms its own specific subfield because of the importance of randomized studies to the approval process of medicinal products. The type of weak instrument considered in noninterventional studies is far weaker than in RCT. The difference in rates of product usage due to prescriber preference may be very low, as it is diluted by other factors, such as patient preference and the heterogeneity of indications. For example, although a specific prescriber might prefer a medicinal product, specific patients will present with medical histories that may suggest alternative treatments or have preferences of their own, perhaps based on previous successful therapy. This can make the instrument quite weak.

Therefore, it requires the use of specialized regression techniques to handle weak instruments, as direct analysis of the instruments will greatly dilute the size of the effect, beyond any useful level. The most basic approach to doing this type of analysis is to use two-stage least squares (2SLS) regression to correct for the weakness of the IV. One limitation of the 2SLS regression is that it can only estimate risk differences with IV and not relative risks. Other approaches do exist to handle dichotomous outcomes for relative measures, although they are less widely used (Rassen et al., 2009a).

A typical approach to conduct a 2SLS regression is to define two separate statistical models that, in conjunction, result in an estimate of the association between the exposure and the outcome of interest. The first model predicts the probability of a patient of a given prescriber being prescribed the product of interest, conditional on the IV, and a vector of baseline covariates. In this model, the IV represents the exposure assigned to the previous patient of the same prescriber and yields coefficients that quantify the association between the IV and the actual exposure in terms of adjusted risk difference.

The second model predicts the outcome of the patient conditional on the probability of exposure to the medicinal product of interest that is estimated in the first model and observed baseline covariates. The IV estimate of the effect of the exposure on the outcome is represented as adjusted risk difference (Abrahamowicz et al., 2011).

These two multiple linear regression estimates can be combined in a number of ways, including the straightforward approach of dividing the estimate from the second model by that of the first. Confidence intervals can be obtained by bootstrapping. Clearly, a very weak instrument could create an unstable estimate (Ionescu-Ittu et al., 2009).

Reference

Essentials of Research Methods in Health, Physical Education, Exercise Science, and Recreation (Point (Lippincott Williams & Wilkins))

Intervention Research and Evidence-Based Quality Improvement, Second Edition: Designing, Conducting, Analyzing, and Funding