Propensity Score Methods for Bias Reduction in Observational Studies of Treatment Effect

Sindhu R. Johnson, MD, PhD[a,b,*], George A. Tomlinson, PhD[b,c,d], Gillian A. Hawker, MD, MSc[b,e], John T. Granton, MD[f,g], Brian M. Feldman, MD, MSc[b,c,h]

KEYWORDS

• Propensity score • Bias • Observational data • Scleroderma • Systemic sclerosis

KEY POINTS

- The absence of randomization in an observational study makes inferences about treatment effect susceptible to confounding by indication.
- Propensity score methods are a strategy to balance observed characteristics.
- Propensity score methods result in a pseudorandomization, facilitating exchangeability. This result allows for a less biased estimation of the effect of a treatment at each value of the propensity score.

Disclosure Statement: None of the authors have any commercial or financial conflicts of interest to disclose.
Dr S. Johnson has been awarded a Canadian Institutes of Health Research New Investigator Award. Dr G. Hawker is supported as the Sir John and Lady Eaton Chair of Medicine. Dr B. Feldman holds the Ho Family Chair in Autoimmune Disease Research.
[a] Division of Rheumatology, Department of Medicine, Toronto Western Hospital, Mount Sinai Hospital, Ground Floor, East Wing, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada; [b] Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, Toronto, Ontario M5T 3M6, Canada; [c] Dalla Lana School of Public Health, University of Toronto, 155 College Street, Toronto, Ontario M5T 3M7, Canada; [d] Department of Medicine, Division of Support, Systems, and Outcomes, Toronto General Research Institute, Toronto General Hospital, Eaton North, 10th Floor, Room 235, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada; [e] Division of Rheumatology, Department of Medicine, Women's College Hospital, 76 Grenville Street, 8th Floor East, Room 815, Toronto, Ontario M5S 1B2, Canada; [f] Division of Respirology, Department of Medicine, Toronto General Hospital, University Health Network, MUNK Building, 11-1170, 200 Elizabeth Avenue, Toronto, Ontario M5G 2C4, Canada; [g] Division of Critical Care Medicine, Department of Medicine, Toronto General Hospital, University Health Network, MUNK Building, 11-1170, 200 Elizabeth Avenue, Toronto, Ontario M5G 2C4, Canada; [h] Division of Rheumatology, Department of Paediatrics, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada
* Corresponding author. Division of Rheumatology, Toronto Western Hospital, Ground Floor, East Wing, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada.
E-mail address: Sindhu.Johnson@uhn.ca

Rheum Dis Clin N Am 44 (2018) 203–213
https://doi.org/10.1016/j.rdc.2018.01.002
rheumatic.theclinics.com

INTRODUCTION

Observational Data

The merits of observational data for the study of uncommon diseases have long been recognized.[1] Whereas the use of narrow inclusion criteria to select subjects for clinical trials can result in a more precise estimation of a treatment effect in a defined group of subjects, observational studies can evaluate the effect of a treatment in a wider population; a wider selection of subjects may result in a different estimate of treatment effect.[2] Thus, observational data may sometimes provide a better representation of the spectrum of real-world practice than conventional randomized trials.[3] Additionally, the use of observational data allows studies to have a longer duration of follow-up. This longer follow-up can yield an important understanding about long-term treatment effects as well as long-term adverse effects. Narrow inclusion criteria and a short follow-up have increasingly been recognized as limitations of clinical trials; there is, accordingly, great value in the use of observational studies, particularly observational cohorts or registries.[1]

Confounding

A challenge to the use of observational data to study treatment effects is the issue of confounding.[4] Confounding of a treatment effect occurs when there is a distortion of the estimated treatment effect on an outcome caused by the presence of another factor.[5] This factor (ie, confounder) must be (1) causally related to the outcome independently of the exposure and (2) associated with the exposure but not a consequence of exposure. The confounder can have a positive influence, increasing the measured treatment effect above what it would otherwise be, or it can have a negative influence, falsely lowering the measured treatment effect.[5] In its simple form, confounding can be considered a confusion or mixing of effects whereby the effect of an exposure is distorted because of the effect of another variable.[6,7]

Confounding by indication (also known as treatment selection bias or susceptibility bias) is a special and important form of confounding that threatens the use of observational data to make unbiased estimates of treatment effect.[5,8] In a randomized trial, the act of randomization ensures that treatment assignment is random. In an observational study, treatment assignment is not random and may be influenced by a variety of factors. Confounding by indication occurs when there is noncomparability between the study groups resulting from the way they were constructed.[5] Exposed and unexposed patients may differ systematically in important characteristics. These characteristics may include disease severity, comorbidity, prognosis, local practice patterns, health care access, and patient preferences.[9,10] Small differences between treatment groups in many covariates can accumulate into substantial overall differences.[3] It may be that these differences have a greater effect on the outcome than the intervention itself. Properly conducted randomized trials are not affected by confounding by indication. Confounding by indication needs to be considered when the interest of an analysis lies in the effect of a treatment that is given in the course of clinical care.

A more nuanced way of thinking about confounding by indication is the use of the counterfactual definition.[5,11] Savitz sets up the counterfactual concept as follows:

> *The ideal comparison group for the exposed group is the exposed group itself but under the condition of not having been exposed, an experience that did not, in fact, occur (thus it is counterfactual). If we could observe this experience (which we cannot), we would be able to compare the disease occurrence under the*