Time-Dependent Confounders: Are They All the Same?

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KEY POINTS . . .

Unlike in randomized clinical trials, assessing treatment effects in observational studies using real-world data comes with analytical challenges mainly with respect to treatment selection bias.

Even in the absence of treatment selection bias at baseline, in cohort studies wherein patients are followed over time, traditional regression methods may yield biased estimates of causal treatment effects, especially in the presence of time-dependent confounders.

However, not all time-dependent confounders are the same. The biased estimates are more likely to occur in the presence of time-dependent confounders *affected by prior treatment* than those *not affected by prior treatment.*

The following article represents the third in a series that highlights local student chapter activities and research talents. In this section, we present the concepts of confounding, treatment assignment, and selection bias in observational research and distinguish two distinct types of time-dependent confounding: (1) time-dependent confounding not affected by prior treatment *and (2) time-dependent confounding* affected by prior treatment.

What Is a Confounder?

A confounder is an extraneous variable that is: (1) associated with the main exposure (independent) variable; (2) associated with the outcome (dependent) variable; and (3) not a mediator (i.e., not in the causal pathway between the main exposure and outcome variables). For example, when examining the relationship between antidepressant use (main exposure variable) and the increased risk of suicidality (main outcome variable), depression is a confounder. Depression is independently associated with both initiating treatment with antidepressants and also with suicidal behavior. In this scenario, one can expect that patients receiving antidepressants are more likely to have depression than patients not receiving antidepressants. Hence, assessing treatment effects in observational studies using real-world data comes with analytical challenges, particularly with respect to treatment selection bias. In spite of these challenges, longitudinal observational studies are a crucial part of post-marketing research to investigate long-term treatment-emergent benefits and risks in real-world populations.

Treatment Assignment and Selection Bias

In randomized clinical trials (RCTs), randomization is conducted based on the presumption that all measured (observed risk factors) and unmeasured (unobserved risk factors) confounders are equally distributed among study treatment arms, satisfying the independence assumption of treatment assignment. Hence, observed differences in treatment effect between the study arms can be directly attributed to a causal treatment effect. However, in observational research using real-world data, this may not be the case since treatment assignment cannot be randomized. Instead, the receipt of treatment is dependent on multiple factors (e.g., patient sociodemographic and clinical characteristics, prescriber preference, etc.), violating the independence assumption of treatment assignment. Nevertheless, as RCTs are often conducted among relatively homogenous patient populations with restrictive inclusion and exclusion criteria, observational studies are useful in generating findings more generalizable to broader patient populations.

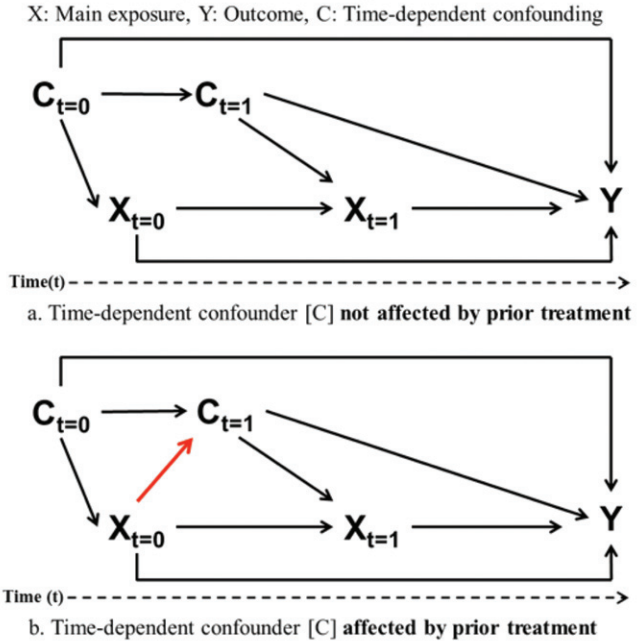
In *certain* cases, time-dependent confounding also acts as a mediator and poses a threat to the internal validity of findings.

Assuming that there is no unmeasured confounding, traditional methods used in observational research including matching, propensity score adjustment, and multivariable regression models can account for selection bias at baseline (i.e., accounting for differences in measured confounding factors between the treated and untreated patient populations). However, given the complexity and dynamic nature of treatment decisions during follow-up, the reinstated independence assumption at baseline is often once again subject to violation at a later time point, especially in the presence of time-dependent confounders.

Time-Dependent Confounding

In epidemiology, a time-dependent confounder is: (1) a covariate that *changes over time* and, also (2) a confounder, meaning that it is associated with both exposure and outcome, and *also not a mediator* in the association between exposure and outcome (i.e., not in the causal pathway). In *certain* cases, time-dependent confounding also acts as a mediator and poses a threat to the validity of findings. There are two distinct types of time-dependent confounders: (1) time-

Figure 1. Time-dependent confounding



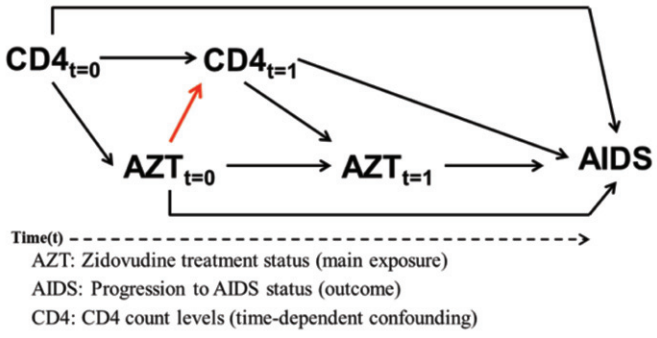
dependent confounding *not affected by prior treatment*, and (2) time-dependent confounding *affected by prior treatment*.

Figure 1a provides an illustration of time-dependent confounding *not affected by prior treatment*, where C is a time-dependent confounder, X is the main exposure variable (treatment), and Y is the study outcome in a hypothetical longitudinal study. C is a confounder because it is associated with outcome Y and also with treatment X at all time points. While $C_{t=1}$ is related to $C_{t=0}$, $C_{t=1}$ is not affected by prior treatment $X_{t=0}$, and therefore is also not a mediator in the association between outcome Y and treatment X_0. In this case, adjusting for C at baseline ($C_{t=0}$) (as well as during follow-up) will not produce biased estimates of treatment effects, under the assumption of no unmeasured confounding, as C (at all time points) satisfies the three epidemiological conditions of a confounding variable. For example, if patient age is a confounder in the association between study treatment and outcome; in longitudinal studies, patient age is a time-dependent confounder *not affected by prior treatment* status as prior treatment does not dictate patient age.

However, this is not the case in the Figure 1b, an illustration of a time-dependent confounder *affected by prior treatment*. While C in this figure is associated with both drug treatment X and with outcome Y at all time points, C at later time points, such as $C_{t=1}$, is affected by prior treatment ($X_{t=0}$), leading $C_{t=1}$ to be in the causal pathway between exposure $X_{t=0}$ and outcome Y. Unlike in Figure 1a, in this scenario, $C_{t=1}$ acts not only as a confounder, but also as a mediator, indicating that traditional methods adjusting for time-dependent covariates, such as time-dependent multivariable Cox model, will produce biased estimates of treatment effects.

Figure 2 provides an example of time-dependent confounding *affected by prior treatment* in a hypothetical longitudinal observational study assessing whether zidovudine treatment slows progression to AIDS (acquired immunodeficiency syndrome) among

Figure 2. CD4 lymphocyte counts as time-dependent confounding affected by prior antiretroviral treatment (e.g., zidovudine)



patients with HIV (human immunodeficiency virus) infection. Zidovudine is a disease modifying antiretroviral HIV treatment usually recommended for patients with >350 CD4-positive T-cells per microliter of blood [1]. CD4 count is a confounder because 1) CD4 count levels determine the receipt of zidovudine treatment, and 2) CD4 count level is a predictor for progression to AIDS. But, among patients initiating treatment with zidovudine, the treatment itself has the potential of lowering CD4 count levels, thereby affecting subsequent treatment decisions. Therefore, CD4 count level (confounder) is affected by prior zidovudine treatment status.

As demonstrated in the Figure 2, CD4 count level is a confounder as it is associated with both zidovudine treatment and progression to AIDS, but also acts as a mediator after treatment initiation as it is affected by prior zidovudine treatment. In the presence of time-dependent confounders affected by prior treatment, treatment effect estimates will be biased in the following analytical scenarios:

(1) When there is no adjustment for confounding (CD4 counts), the crude estimates for treatment effect will be biased because zidovudine treatment assignment is not independent and contingent upon CD4 count levels.
(2) When there is an adjustment only for baseline CD4 count levels, but not for subsequent CD4 count levels, the estimates for treatment effect will still be biased. While this approach adjusts for treatment selection at baseline, it does not address treatment selection at later time points. It disregards the fact that HIV patients who initiated treatment at later time points will be those whose CD4 count levels worsened as compared with patients who are yet to initiate treatment.
(3) Finally, when there is an adjustment for CD4 count levels at baseline and also at later time points during follow-up, the results will still be biased as zidovudine treatment will partially improve CD4 count levels. Therefore, at later time points, CD4 count level also becomes a mediator in the causal pathway between zidovudine treatment and progression to AIDS. Over-adjustment bias due to adjustment of mediators has been well-documented and illustrated in the literature. Controlling for a time-dependent confounder affected by prior treatment using traditional analytical methods will result in inconsistent estimates of true treatment effects [2,3]. Robin and colleagues introduced marginal structural modeling methodology employing inverse-probability-of-treatment-weights in longitudinal observational studies to account for mediation effect of time-dependent confounders in the association between the main independent variable and main outcome variable [4,5].

Conclusion: Not All Time-dependant Cofounders are the Same

RCTs that randomly assign patients to treatment arms are often considered the "gold-standard" in assessing the effectiveness, safety, and tolerability of medical interventions. However, in observational research using real-world data, randomization is not feasible and, thus, treatment selection is often subject to confounding by indication. Even in the absence of treatment selection bias at *baseline*, traditional methods may yield biased estimates of causal treatment effects, especially in the presence of time-dependent confounders. *However, not all time-dependent confounders are the same.* The biased estimates are more likely to occur in the presence of time-dependent confounders *affected by prior treatment* than those *not affected by prior treatment*.

References

[1] World Health Organization. New HIV recommendations to improve health, reduce infections and save lives. Available at: http://www.who.int/mediacentre/news/releases/2009/world_aids_20091130/en/index.html. [Accessed March 11, 2016]. [2] Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiol 2009;20:488-95. [3] VanderWeele TJ. On the relative nature of overadjustment and unnecessary adjustment. Epidemiol 2009;20:496-9. [4] Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiol 2000;11:550-60. [5] Ali AK. Causal inference from observational data with time-dependent confounding: application of marginal structural models for multi-category exposures. ISPOR Connections, March-April 2013. Available at: http://www.ispor.org/news/articles/march-april13/casual-inference.asp. [Accessed March 11, 2016]. ■

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