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Brian L. Egleston, *Fox Chase Cancer Center*

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Response to Pearl's Comments on Principal Stratification

Brian L. Eggleston

Abstract

Dr. Pearl invites researchers to justify their use of principal stratification. This comment explains how the use of principal stratification simplified a complex mediational problem encountered when evaluating a smoking cessation intervention's effect on reducing smoking withdrawal symptoms.

KEYWORDS: causal inference, principal stratification, mediation, smoking cessation interventions

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Dr. Pearl's paper, "Principal Stratification - A Goal or a Tool", challenges researchers to justify their use of this method. One concern that Dr. Pearl raises is that principal stratification is of limited use in investigating mediational pathways. He argues that it may not be meaningful to condition on the values that intermediate variable potential outcomes happen to take. Instead, one should conceptualize what would happen if one were able to manipulate the intermediate variable.

I agree with Dr. Pearl that principal stratification might have limited utility in investigations where manipulation of all variables in a causal pathway is possible. However, I believe that principal stratification has simplified many research questions that had seemed intractable. In particular, principal stratification can bring clarity to research questions among human subjects where manipulation is not possible either for ethical or practical reasons. Principal stratification offers the possibility of redefining complex mediational questions into simpler easy to test hypotheses that bring greater clarity to the issue at hand.

For example, I recently used principal stratification in an investigation of the effect of a smoking cessation intervention on smoking withdrawal symptoms (Egleston et al., 2010). The intervention arm in the study received nicotine replacement therapy with a behavioral intervention. The control arm received no intervention. While the primary objective of smoking cessation interventions is generally to help individuals quit smoking, an important secondary objective is to reduce withdrawal symptoms during the quitting process. All else being equal, if two different interventions are able to achieve comparable quit rates among smokers, the intervention that is more successful in reducing withdrawal symptoms would be preferable.

One concern with investigating the effect of the intervention on withdrawal symptoms is the complicating role of whether a person becomes abstinent and quits smoking during the study. Logically, those who do not attempt to quit will not have smoking withdrawal symptoms. Hence, an analysis that naively examines the impact of the intervention on withdrawal symptoms might incorrectly conclude that the intervention worsens symptoms. The intervention, however, might have no direct effect on withdrawal symptoms, but instead, might only impact symptoms through its impact on smoking abstinence. Subject matter experts have noted this problem and issued guidance recommending that smoking withdrawal symptoms only be investigated among those observed to abstain in a study (Shiffman et al., 2004). Since abstinence is a post-randomization variable, we can show that examining intervention effects within those stratified by observed abstinence status, as recommended (Shiffman et al., 2004), is flawed (Egleston et al., 2010; Pearl, 2009; Cole and Hernán, 2002; Imai et al., 2010).

The typical mediational pathway does not work well in this case as there could be circularity in the causal pathway. It is possible that a smoking cessation

intervention impacts withdrawal symptoms which in turn impacts the ability of someone to quit smoking. However, it is also possible that a smoking cessation intervention impacts smoking abstinence which in turn affects whether someone has symptoms. The causal chain is unclear here. Which is the mediator in this context: withdrawal symptoms or smoking abstinence?

Rather than using the typical mediational model described by Imai and colleagues (2010), we instead redefined the problem in a way that more readily addressed the issue at hand: is there evidence that smoking cessation interventions affect withdrawal symptoms. To do this, we decided to look at the effect of the intervention in the principal stratum consisting of those who would abstain regardless of intervention assignment. In this group, the complicating factor of abstinence could be controlled, and we could indeed see that the intervention did reduce symptoms.

Throughout the project, I deliberately avoided using the term "mediator" to describe abstinence. I think a more appropriate term might be a post-randomization confounder because the direction of the mediational pathway is unclear, and not central to our investigation.

The use of principal stratification came from the desire to simplify a problem for a clinical audience. Clinicians are used to examining subgroup effects, and hence an effect of an intervention within the subgroup of "always abstainers" was easy to comprehend. Further, it was intuitive for clinicians to understand how such an analysis removed the complicating factor of smoking abstinence. Had we instead treated the issue as a traditional mediational problem, it is unclear whether many clinicians would have found the interpretation of the findings as meaningful. Finally, abstainers had already been specified as a subgroup of interest for withdrawal symptom studies by researchers in the field (Shiffman et al., 2004)

If the study had only included mice, principal stratification might not have been necessary. The investigators could have randomized both the intervention and abstinence to obtain Dr. Pearl's preferred direct and indirect effects.

I believe that one strength of principal stratification is its ability to simplify complex questions for clinical investigators. In the past, we have seen the use of new methods such as propensity scores (Rosenbaum and Rubin, 1983) proliferate for the same reason. By using propensity scores, investigators no longer needed to examine regression models with ancillary parameters that complicate interpretation. Similarly, I believe that principal stratification has a bright future as a tool for providing insight into complex clinical problems.

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