# Confounding Adjustment and Exposure Prediction in Environmental Epidemiology: Additional Insights

***To the Editor:***

In our recent article,[1] we discuss the interplay between confounding adjustment and exposure prediction in environmental epidemiology. We focus on a 2-stage approach where the exposure is predicted in the first stage and the estimated exposure from the first stage is used as a known covariate in a second-stage health-effect regression model. In this 2-stage approach, there is always uncertainty about the exact set of confounders that must be included into the health-effect regression model. We argue that (1) the exposure prediction stage can be beneficial or detrimental when the goal of the study is health-effect estimation; (2) it is dependent on which covariates are included in the health-effects regression model to control confounding. Several special cases are discussed, and all analytic results are left to the eAppendix.

Szpiro and colleagues[2–4] have been conducting a similar line of research. Specifically, they (1) demonstrate that more accurate exposure prediction does not necessarily improve health-effect estimation,[2] (2) provide an analytic solution for correction of measurement error with spatially misaligned data,[3] and (3) discuss confounding and measurement error in the context of air pollution epidemiology.[4]

In our article on EPIDEMIOLOGY, we inadvertently omitted their latest contribution,[5] which is closely related to our work. Szpiro and Paciorek[5] propose an analytic framework for describing the complex measurement error that is induced when a 2-stage approach is used in environmental epidemiology. In Section 2.3, they provide 2 conditions that need to be satisfied in the first-stage exposure prediction model to guarantee consistent estimation of a health effect in the second stage.

According to Szpiro and Paciorek,[5(p 504)] condition 1 is that the spatial distribution of the covariates must be the same at the monitoring locations and at the subject locations. We made the stronger assumption that the regression coefficients from the exposure prediction model are known exactly. This can be interpreted as a combination of infinite monitoring data, along with condition 1.[5]

Szpiro and Paciorek[5(p 504)] further propose condition 2, which states that the covariates and basis functions used in the exposure prediction model must include the spatially structured components of the covariates in the health-effect model. This condition is related to our results in the section titled "Confounding Bias Due to Exposure Prediction Under Exposure Prediction Model Misspecification."[1(p 585)] We report that under a correctly specified health-effects regression model, using a predicted exposure will bias the health-effect estimate unless (1) the exposure prediction model is correctly specified, (2) the covariates used in the exposure prediction are uncorrelated with the confounders in the health-effect model, or (3) all the true confounders are included in the exposure prediction model. This third condition is a simplified version of condition 2 of Szpiro and Paciorek.[5(p 504)]

One important difference between our results and the results of Szpiro and Paciorek[5] is that they assume the health effect of interest is the coefficient from whatever health-effect regression model is specified. In other words, all their results are conditional on a prespecified health-effect regression model that does not necessarily fully adjust for confounding. In our work, instead, we report our results under a situation where we target the health effect from a correctly specified health-effect regression model. This difference allowed us to consider situations where both confounder selection and exposure prediction are needed.

In observational studies, there is inherent uncertainty in how to properly adjust for confounding, and we have explored the interplay between exposure prediction and confounding adjustment. Our results, along with those of Szpiro and Paciorek,[5] highlight the fact that exposure prediction and confounding adjustment need to be considered simultaneously.

We are thankful to Drs. Szpiro and Paciorek for their important contributions on this topic and thankful to the Editor for giving us the opportunity to tie together these 2 important contributions in the literature.

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# Three Approaches to Causal Inference in Regression Discontinuity Designs

***To the Editors:***

Regression discontinuity designs offer a rigorous approach to causal inference when an exposure is assigned

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(at least in part) by a threshold rule on a continuous assignment variable. For example, antiretroviral therapy is prescribed for HIV patients when their CD4 count falls below some threshold.[1] Treatment assignment based on a threshold rule leads to a natural experiment: for a subpopulation of patients, both potential outcome means — $E[Y(1)]$ if treated, $E[Y(0)]$ if not treated — can be estimated. We have recently published an introduction to regression discontinuity for epidemiologists and a clinical application in this journal.[1] In their thoughtful commentary on our article,[1] Vandenbroucke and le Cessie write that regression discontinuity "may produce valid causal inferences, at least under some assumptions."[2p738] We would like to comment on the nature of the assumptions required for causal inference in regression discontinuity designs, as there has been considerable historical evolution in perspectives on this matter.[3] We describe three distinct approaches to inference in regression discontinuity designs, listed in order from the strongest (least plausible) to weakest (most easily met) assumptions required. The differences in these approaches turn on the assumptions made about the potential outcome conditional expectation functions (POCEFs) — $E[Y(1)|Z]$ and $E[Y(0)|Z]$ — which describe how the potential outcome means change with the assignment variable, $Z$.

(1) *Extrapolation across the full range of Z (functional form assumption)*. Assumptions about the full functional form of the POCEFs enable identification of a global average causal effect by extrapolating the POCEFs into unobserved regions and estimating the difference in POCEFs across all values of $Z$ (eg, Rubin).[4] This estimand is analogous to the parameter that would be estimated in a randomized controlled trial for the same population. Vandenbroucke and le Cessie[2] describe one case in which such an assumption may be justified: if $Z$ and $Y(1)$ and $Z$ and $Y(0)$ are jointly normally distributed, then $E[Y(1)|Z]$ and $E[Y(0)|Z]$ will be linear (and known). In general, however, assumptions about the shape of the unobserved POCEFs are strong and untestable. Guess wrong about functional form, and effect estimates will be biased.

(2) *Extrapolation at the cut-off (continuity assumption)*. Most recent literature on regression discontinuity design (eg, cited in Lee and Lemieux)[5] seeks to estimate a "local" (rather than global) causal effect. Rather than extrapolating the unobserved POCEFs across the full range of $Z$, this approach requires extrapolation only across an arbitrarily small region at the cut-off. In place of strong functional form assumptions, local inference requires only that the POCEFs are continuous at the threshold. Continuity implies that within a small neighborhood around the threshold, potential outcomes are independent of treatment assignment, just as in an randomized controlled trial. Local linear regression provides a consistent method for inference.[6] Although continuity at the threshold is a weak assumption, it is still an assumption: if another exposure coincided precisely with the threshold rule, then effect of the treatment would be confounded. For example, date of birth may determine eligibility for a public program, but also reflect contextual factors that determined fertility patterns in the previous generation. The design, however, rules out many of the common confounders in observational studies, which would likely be continuous in $Z$. Continuity in baseline observables can increase confidence in the assumption that the POCEFs are indeed continuous at the threshold.

(3) *No precise manipulation of the assignment variable*. In some applications, even the relatively weak assumption of continuous POCEFs is not required for identification of local causal effects. Specifically, when there is random noise in measurements of the assignment variable *and* patients (or providers) cannot precisely manipulate the value of the assignment variable (eg, to gain access to treatment), then patients close to the threshold will be randomly allocated to being above versus below the threshold and continuity will be guaranteed in expectation.[5] The presence of manipulation can be assessed in the data,[7] and so one might question whether an assumption that can be tested should even be called an assumption. When there is no systematic manipulation, even the weak unconfoundedness assumption required in (2) is no longer required. Under this third approach to inference, "local randomization" is achieved by virtue of the data-generating process: a true natural experiment.[8] It is this interpretation that has given the regression discontinuity design its reputation as the "next best thing after a randomized trial."[2p738]

The "local randomization" interpretation obtained from approach (3) may be justified in many clinical applications. For example, in our application, CD4 counts are measured with noise. For patients with true CD4 counts close to the threshold, random noise randomizes patients to treatment eligibility or ineligibility; CD4 counts were obtained directly from the lab and we found no evidence of systematic manipulation.[1] In applications, where the assignment variable is measured without much error (eg, height, age, or geographic location), threshold rules still yield plausible natural experiments, which can be analyzed using regression discontinuity designs under the stronger assumption of continuity in POCEFs at the cut-off, approach (2). In a departure from some of the earlier regression discontinuity literature cited by Vandenbroucke and le Cessie[2] most recent regression


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discontinuity studies[5] have eschewed the strong assumptions required for inference on global causal effects, ie approach (1), in favor of *local* inference at the threshold, ie approaches (2) and (3). Generalizability to other (sub-) populations (eg, to obtain a global causal effect) is then a matter of external—not internal—validity. Regardless of the approach to causal inference, the causal parameter estimated and the assumptions required for a causal interpretation should be clearly stated in all regression discontinuity applications.[9]

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***The authors respond:***

Bor et al[1] should be commended for succinctly clarifying the nature and the assumptions behind the different forms of the "regression discontinuity designs" in their response to our commentary. It might be good to add which aspects of a randomized clinical trial (RCT) are mimicked in the various situations that they describe. The first situation necessitates complete and exact knowledge of the regression lines in all treated and untreated persons. This is the situation that needs the strongest assumption, but it is also the situation in which the inference may come closest to that of an RCT because the treatment effects are averaged over a wide range of values that are of interest. Situations 2 and 3 have fewer assumptions, but there is a price to pay: the inference is now about a local effect around the threshold. Situation 3 seems most attractive, as the idea of "an allocation as good as random" holds, which comes close to the pivotal mechanism that makes RCTs stand out. However, that will happen only very close to the threshold—and it is likely that, in most data sets, estimation will need rather wide windows around the threshold, which makes it uncertain whether exchangeability still holds. This third situation might be subject to potential drawbacks similar to those of instrumental variable analysis, which also primarily estimates a local average treatment effect[2]—eg, by needing much larger numbers than conventional analysis.[3] We hope that this exchange will lead to further attempts at application of the diverse forms of "regression discontinuity" to clarify its usefulness and its drawbacks.

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# ERRATUM

**Does exposure prediction bias health-effect estimation? The relationship between confounding adjustment and exposure prediction: Erratum**

Reference

Cefalu M, Dominici F. Does exposure prediction bias health-effect estimation?: The relationship between confounding adjustment and exposure prediction. *Epidemiology.* 2014;25:583–590.

The following reference was inadvertently omitted:

Szpiro AA, Paciorek CJ. Measurement error in two-stage analyses, with application to air pollution epidemiology. *Environmetrics*. 2013;24:501–517.

A letter from Drs. Cefalu and Dominici in this issue of the journal discusses further extensions on this topic.