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Toward a Clearer Portrayal of Confounding Bias in Instrumental Variable Applications

John W. Jackson^{#1,2} and Sonja A. Swanson^{#1}

¹ Harvard T.H. Chan School of Public Health, Department of Epidemiology, Boston, MA

² Brigham and Women's Hospital, Department of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Boston, MA

[#] These authors contributed equally to this work.

Abstract

Recommendations for reporting instrumental variable analyses often include presenting the balance of covariates across levels of the proposed instrument and levels of the treatment. However, such presentation can be misleading as relatively small imbalances among covariates across levels of the instrument can result in greater bias due to bias amplification. We introduce bias plots and bias component plots as alternative tools for understanding biases in instrumental variable analyses. Using previously published data on proposed preference-based, geography-based, and distance-based instruments, we demonstrate why presenting covariate balance alone can be problematic, and how bias component plots can provide more accurate context for bias due to omitting a covariate from an instrumental variable versus non-instrumental variable analysis. These plots can also provide relevant comparisons of different proposed instruments considered in the same data. Adaptable code is provided for creating the plots.

Keywords

confounding; bias; instrumental variable; covariate balance

Introduction

Instrumental variable methods have been increasingly used to estimate causal effects in observational studies.¹⁻³ Such methods require investigators to propose a pre-treatment variable, known as an instrument, that meets three conditions: (1) it is associated with treatment, (2) any effect it has on the outcome is fully mediated by treatment, and (3) it shares no causes with the outcome.⁴⁻⁶ Point-identifying the average treatment effect with the standard instrumental variable estimator further assumes additive effect homogeneity. While condition (1) can be empirically verified, conditions (2) and (3) cannot. Under some circumstances, these conditions can be rejected;⁷ otherwise, investigators need to use subject

Corresponding author: Sonja A. Swanson, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Kresge 9th Floor, Boston, MA 02115, 651.270.9984, sswanson@hsph.harvard.edu.

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matter knowledge to justify their potential appropriateness. While the popularity of instrumental variable methods is no doubt due to their ability to identify causal effects even in the presence of unmeasured confounding, we see that this promise comes with a cost: instrumental variable methods shift the problem of knowing, measuring, and appropriately adjusting for confounders of the treatment–outcome relationship to confounders of the instrument–outcome relationship, i.e., to satisfy condition (3).

In recognizing this trade-off, investigators have repurposed tactics for assessing and understanding potential treatment–outcome confounding to instrument–outcome confounding. One commonly proposed^{2,8,9} and implemented¹⁰⁻¹⁵ strategy is to assess the balance of measured covariates across levels of treatment and levels of the instrument, e.g., by displaying a table of the prevalence differences of measured covariates by the treatment and proposed instrument. As with other covariate balance diagnostic assessments, these tables are intended to illuminate whether there are large imbalances in measured covariates (which could be accounted for through statistical adjustment) that may signal potential confounding by unmeasured covariates. Moreover, this particular approach is intended to provide context for whether the no-unmeasured-confounding assumption is more likely to hold for an instrumental variable analysis than for a non-instrumental variable analysis. However, these simple diagnostics could lead to misinterpretations because the bias due to a violation of condition (3) is amplified when the proposed instrument is not strongly associated with the treatment. As such, an instrumental variable analysis could be more biased than a non-instrumental variable analysis even when the covariates appear to be better balanced by the proposed instrument than by the treatment. While methods have been proposed that incorporate this bias amplification,¹⁶ such methods have rarely been adopted and comparing the covariate balance directly has evolved as common practice.

In the current study, we augment the practice of presenting covariate balance by the proposed instrument in a way that accounts for the bias amplification. We begin by briefly reviewing the magnitude and direction of confounding bias in both a non-instrumental variable and an instrumental variable analysis. We then present a refined approach for displaying either the full bias or augmented covariate balance, and describe how this approach could be used to assess the validity of a single proposed instrument, and to inform the decision between two or more proposed instruments. This follows in the tradition of using graphical approaches for diagnostic assessments, an arguably preferable strategy to tabular presentations.^{17,18} Examples are drawn from published studies, and relevant R code (using the ggplot2 package¹⁹) is provided in the online Supplementary Materials.

Notation and Terminology

We draw from the sensitivity analysis literature to isolate the bias due to unmeasured confounding for an instrumental variable and a non-instrumental variable analysis in identifying the average treatment effect. We consider a binary proposed instrument Z (0=no vs. 1=yes), binary treatment X (0=no vs. 1=yes), binary or continuous outcome Y , and an unmeasured binary confounder U of both the X - Y and Z - Y relationships. The average potential outcome Y had all subjects received treatment level $X=x$ is noted as $E[Y(x)]$. Our interest is in identifying the average treatment effect, $E[Y(x=1)]-E[Y(x=0)]$. Throughout, we

assume the first two instrumental conditions hold: i.e., that Z is associated with X (either because Z causes X directly or is a measured proxy for an unmeasured causal instrument) and that Z causes Y only through X (if at all).

We reproduce results presented by Brookhart and Schneeweiss¹⁶ and Baiocchi et al.⁹ for bias in both the instrumental variable and non-instrumental variable analyses. Their derivations use a linear structural model that we describe in the following section.

Confounding Bias for a Non-Instrumental Variable Estimator

Consider the following linear structural model, where α_1 is the treatment effect within levels of U and by our assumption of no additive effect modification by U (further implied by the omission of a product term) also the average treatment effect.

$$Y(x) = \alpha_0 + \alpha_1 x + \alpha_2 U + \epsilon_x$$

Assume that the mean of the error term is 0. Suppose we proposed to use the crude risk difference as a non-instrumental variable estimator. This bias in the estimator failing to condition on U can be derived as follows:

$$\begin{aligned} & E[Y(x=1)] - E[Y(x=0)] - E[Y|X=1] - E[Y|X=0] \\ &= \alpha_1 - (E[Y|X=1] - E[Y|X=0]) \\ &= \alpha_1 - (E[\alpha_0 + \alpha_1 X + \alpha_2 U + \epsilon_0 + X(\epsilon_1 - \epsilon_0)|X=1] - E[\alpha_0 + \alpha_1 X + \alpha_2 U + \epsilon_0 + X(\epsilon_1 - \epsilon_0)|X=0]) \\ &= \alpha_2 (E[U|X=1] - E[U|X=0]) \\ &= (E[Y|U=1, X=x] - E[Y|U=0, X=x]) (E[U|X=1] - E[U|X=0]) \end{aligned}$$

Note $E[\epsilon_0 + X(\epsilon_1 - \epsilon_0)|X] = 0$ by iterated expectations, and the rest follows algebraically by equivalence statements. Thus, bias due to confounding is a product of (i) the difference in mean outcomes across levels of U conditional on X , and (ii) the prevalence difference in covariate U across treatment X .

Confounding Bias for the Standard Instrumental Variable Estimator

Under the same linear structural model, we can also derive bias in the standard instrumental variable estimator:

$$\begin{aligned} & E[Y(x=1)] - E[Y(x=0)] - \frac{E[Y|Z=1] - E[Y|Z=0]}{E[X|Z=1] - E[X|Z=0]} \\ &= \alpha_1 - \frac{E[Y|Z=1] - E[Y|Z=0]}{E[X|Z=1] - E[X|Z=0]} \\ &= \alpha_1 - \frac{E[\alpha_0 + \alpha_1 X + \alpha_2 U + \epsilon_0 + X(\epsilon_1 - \epsilon_0)|Z=1] - E[\alpha_0 + \alpha_1 X + \alpha_2 U + \epsilon_0 + X(\epsilon_1 - \epsilon_0)|Z=0]}{E[X|Z=1] - E[X|Z=0]} \\ &= \alpha_1 - \frac{\alpha_1(E[X|Z=1] - E[X|Z=0]) - \alpha_2(E[U|Z=1] - E[U|Z=0])}{E[X|Z=1] - E[X|Z=0]} \\ &= \alpha_2 \frac{E[U|Z=1] - E[U|Z=0]}{E[X|Z=1] - E[X|Z=0]} \\ &= (E[Y|U=1, X=x] - E[Y|U=0, X=x]) \frac{E[U|Z=1] - E[U|Z=0]}{E[X|Z=1] - E[X|Z=0]} \end{aligned}$$

Note assuming Z only causes Y through X implies $E[\epsilon_0|Z] = 0$, and $\epsilon_1 - \epsilon_0 = 0$ by a constant treatment effect condition (we can also use a slightly weaker but more opaque

assumption that $E[X(\epsilon_1 - \epsilon_0)|Z = z] = 0$; the rest follows algebraically by equivalence statements. Thus, the bias due to confounding of the instrument is the product of (i) the difference in mean outcome across levels of U conditional on X , and (ii) the prevalence difference in covariate U across the instrument Z , divided by (iii) the prevalence difference of treatment X across instrument Z . We will refer to $1/(E[X|Z=1] - E[X|Z=0])$ as a “scaling factor” which amplifies the bias when the instrument-outcome relationship suffers from unmeasured confounding.⁴

Bias Components and Covariate Balance

To compare the bias between an instrumental variable analysis and a non-instrumental variable analysis that both fail to appropriately adjust for U , it is sufficient to compare the non-shared bias components. Both expressions include a component reflecting the relationship between U and Y within levels of X ; , we can therefore evaluate the relative bias due to omitting U from either analysis by comparing the covariate prevalence difference by treatment and by the proposed instrument multiplied by our scaling factor:

$$E[U|X=1] - E[U|X=0]$$

vs.

$$\frac{E[U|Z=1] - E[U|Z=0]}{E[X|Z=1] - E[X|Z=0]}$$

Note the common approach of presenting measured covariate prevalence differences alongside each other (without the scaling factor) misses a key component of the relative bias. Since $E[X|Z=1] - E[X|Z=0]$ is bounded between 0 and 1, such a comparison will always underestimate the relative bias of omitting the covariate from an instrumental variable analysis versus a non-instrumental variable analysis. Another important insight is that such comparisons of covariate balance assessments only are meaningful under homogeneity conditions: if we had not made any homogeneity assumptions, the bias expressions would not necessarily have covariate balance as a bias component (see online supplementary materials).

Alternatively, investigators have proposed direct comparisons of the bias components, e.g., by presenting bias ratios, $((E[U|Z=1] - E[U|Z=0]) / (E[X|Z=1] - E[X|Z=0])) / (E[U|X=1] - E[U|X=0])$, that represent the relative magnitude of confounding bias between the two approaches.^{9,16} Such approaches are methodologically sound, but may not readily elicit patterns when considering many measured covariates, and only provide context on relative and not absolute bias. The scaled graphical approach presented in the current study retains the spirit of bias ratios, but by using a graphical display of the information should prove more useful and easily interpretable. Specifically, we propose plotting the covariate balance by treatment alongside the scaled covariate balance by the proposed instrument.

Bias Component Plots: Assessing the Validity of Instrumental Variable vs. Non-Instrumental Variable Analyses

We first considered the canonical example of an instrumental variable analysis in epidemiology: a study by McClellan et al.¹² of the effect of intensive myocardial infarction treatments on mortality using a distance-based instrument (often considered the first instrumental variable analysis in epidemiology). McClellan et al. included a table comparing prevalence differences of pertinent measured covariates by levels of treatment and levels of the proposed instrument. We reproduced this table in Figure 1a (i.e., without scaling). All covariates they considered were better balanced across levels of the instrument relative to treatment; the investigators used this to justify the validity of the instrumental variable approach. We next plotted the bias components described above, i.e., the prevalence differences for the treatment axis and the prevalence differences for the proposed instrument multiplied by the scaling factor of $1/0.067$ (Figure 1b; R code provided in the Supplementary Materials). For five of the nine measured covariates presented, there would be more bias incurred due to omitting the covariate from adjustment in an instrumental variable analysis than a non-instrumental variable analysis. In some instances, the bias would be in opposing directions.

We also estimated bias ratios for the nine measured covariates (Table 1). Similar to our plots, we would conclude that for five of the nine measured covariates presented, there would be more bias incurred in an instrumental variable analysis that omits the variable than in a non-instrumental variable analysis (because the bias ratio would be >1 or <-1). By the sign of the bias ratio, we would also know whether the bias would go in opposing directions. However, the bias component plots provide some further context. First, the bias ratios for sex and diabetes status are relatively similar, yet we see in our plot that the bias components for sex are much larger than those for diabetes status; if these covariates were similarly associated with the outcome (on the additive scale), then omitting sex from the analysis would result in more bias than omitting diabetes status in both an instrumental variable and a non-instrumental variable analysis, which we would not detect in comparing the bias ratios. Second, the bias ratios only inform us to the relative direction of bias; if the direction of the association between the covariate and outcome were known, our approach would provide the direction of bias for both an instrumental variable and non-instrumental variable analysis, not just whether the direction aligned. Finally, the visual display allows readers to quickly interpret the data on bias components especially in the setting of many covariates.

Bias Component Plots: Comparing the Validity of Multiple Proposed Instruments

Often comparing the potential validity of two or more proposed instruments is of interest, especially when new instruments are developed or investigators are considering several options. Bias component plots can also aid this endeavor. Consider the study by Fang et al.²⁰ to evaluate the performance of physician practice style measures as instruments for the effect of thiazide diuretic use vs. non-use in patients with hypertension. The authors evaluated one preference-based instrument and two geography-based instruments (driving

area clinical care and primary care service areas),²¹ and concluded that measured covariates were similarly balanced across levels of each of these instruments (Figure 2). However, after applying the scaling factors (1/0.045 for preference, 1/0.188 for driving area clinical care, and 1/0.160 for primary care service areas), the geography-based instrumental variable analyses would often be less biased than the preference-based instrumental variable analysis when a covariate is omitted (Figure 3); for some of the covariates, all three instrumental variable analyses would be more biased than the corresponding non-instrumental variable analysis were that covariate omitted.

Discussion

As in any method, appropriate implementation of an instrumental variable analysis requires epidemiologists to be critical of the underlying assumptions and vigilant in understanding possible biases. Covariate balance assessments are useful diagnostic tools in propensity score methods and have recently been extended to diagnose time-dependent confounding, and evaluate how well sophisticated methods for studying joint and time-varying exposures emulate sequentially randomized trials.^{22,23} The current study demonstrates that covariate balance alone is insufficient and sometimes misleading in understanding confounding bias in instrumental variable methods. We have further shown how the practice of presenting bias component plots or bias plots can provide more accurate diagnostics for instrumental variable analyses.

The proposed plots do not present any measures of statistical uncertainty for the bias components or the implicit comparison between the biases in the non-instrumental variable versus instrumental variable analyses. Extensions that address statistical uncertainty may be feasible but would depend on the investigator's specific underlying analytic questions. At the stage when one is deciding whether an instrumental variable versus a non-instrumental variable approach would be more appropriate, one might pursue estimation techniques for the ratio of or difference between the bias or non-shared bias components (e.g., via bootstrapping). An attractive option would be to simultaneously integrate prior knowledge and statistical uncertainty for each component of full bias expressions, and possibly other threats to validity. Semi-Bayesian and Bayesian approaches to integrating these sources of uncertainty have been developed for confounding bias in non-instrumental variable analysis,²⁴ and similar methods may prove to be helpful for instrumental variable analyses but have not yet been proposed. When considering any of these options, recall that the commonly used two-stage least-squares estimator is consistent but not unbiased. The bias formulas for confounding presented here and elsewhere may not be ill-suited to small samples as these will also be prone to so-called "finite sample" biases, particularly in the case of weak proposed instruments.^{25,26}

Some caveats are in order. While these plots may signal important measured covariates to adjust for in statistical models, and may suggest whether an instrumental variable or a non-instrumental variable analysis would be more biased with respect to omitting measured covariates from the analyses, they are only informative to potential bias when the type of unmeasured confounding expected is similar to that we observe. Like others before,^{2,9,27} we reiterate that assessing covariate balance or comparing the relative bias of methods cannot

prove or disprove whether an instrumental variable (or non-instrumental variable) approach is valid. Moreover, while this tool focuses on common causes as a source of a non-causal association between the instrument and outcome, instrumental variable analyses selecting on treatment (e.g., comparing two active treatments) are prone to a selection bias not explicitly addressed here.²⁸ A further subtle issue is that when covariates are highly correlated, the patterns seen in covariate balance tables, bias ratios, bias component plots, or bias plots may be less informative for understanding the aggregate bias. With bias ratios or bias component plots, investigators may consider adapting summary balance metrics²⁹ that reflect such correlations; for full bias it may be preferable to simply adjust the estimates for other measured covariates. Finally, many investigators conducting instrumental variable analyses express interest in the local average treatment effect or the effect in the so-called “compliers” (under a monotonicity assumption).^{3,30} Covariate balance, bias ratios, and bias component plots are only relevant to this estimand under the strong assumption that the “compliers” are exchangeable with the full study population. Thus, when the local average treatment effect is targeted, reporting covariate balance in the full population is not necessarily relevant to understanding confounding bias in the instrumental variable analysis. Moreover, it is of questionable value to compare the bias for different estimands.

As demonstrated here, these plots can be created not just by investigators but also by readers whenever simple summary data is provided: the prevalence of relevant covariates at each treatment level and instrument level, and the prevalence of the treatment for each instrument level. Unfortunately, while presenting such information has been repeatedly recommended,^{1-4,9,16} it seldom appears in published reports. Covariates likely to be relevant to the instrument–outcome relationship are rarely reported on,³¹ and the strength of proposed instruments is often described with F-statistics or related values while omitting the proportion who received treatment at each instrument level as would be relevant here.³

Confounding and other sources of bias in instrumental variable analyses have been increasingly discussed in the epidemiologic literature.^{1-4,9,16,30} Indeed, multiple reporting guidelines have been recently published in this³ and other^{9,32} medical research journals. Some of these guidelines have advocated for reporting covariate balance as a means to evaluate the validity of the instrumental variable assumptions.^{2,8,9,32} As we have seen in the current study, however, this practice can produce a false sense of security to investigators and readers alike. Unfortunately, it is not yet clear if there is a universal tool to fill this much needed gap. We also recognize the inherent tension between transparent versus succinct reporting for epidemiologic analyses. Nonetheless, we hope the plots presented here provide a useful option for researchers and consumers of research to assess instrumental variable conditions for themselves. We hope that, at minimum, this study serves as an opportunity to continue the much-needed discussion on making potential biases in instrumental variable analyses less opaque.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Covariate balance (bias component) by levels of the treatment and levels of the proposed instrument using summary data published in the study by McClellan et al.¹², (a) unscaled and (b) scaled by the strength of the proposed instrument. A covariate is balanced when the bias component has a value of zero (x-axis).

*Covariates are sorted by balance across treatment. We omitted the covariate urbanicity from this plot because the scaled IV bias component (−6.9) was substantially larger than the treatment and scaled IV bias components for other covariates; see R code in online supplementary materials for details.

Figure 2.

Unscaled covariate balance (bias component) by levels of the treatment and levels of three proposed instruments using summary data published in the study by Fang et al.^{15*}

*Both geography-based instruments were defined using quartiles. For these, the authors compared prevalence differences of the covariates for those in the highest vs. lowest quartile in tabular format, as we repeat here graphically. Covariates are sorted by balance across treatment, and to aid readability, we present only one reference level for the categorical covariates age, poverty, and number of antihypertensive drugs; see R code in online supplementary materials for details.

Figure 3.

Scaled covariate balance (bias component) by levels of the treatment and levels of three proposed instruments using summary data published in the study by Fang et al.^{15*}

*Both geography-based instruments were defined using quartiles. For these, the authors compared prevalence differences of the covariates for those in the highest vs. lowest quartile in tabular format, as we repeat here graphically. Covariates are sorted by balance across treatment, and to aid readability, we present only one reference level for the categorical covariates age, poverty, and number of antihypertensive drugs; see R code in online supplementary materials for details.

Table 1Bias ratios in the study by McClellan et al.¹²

Covariate	Bias Ratio
Urbanicity	-163.1
Race	-24.6
Sex	-1.9
Diabetes	-1.2
Renal Disease	-0.9
Dementia	-0.7
Cancer	0.0
Cerebrovascular Disease	0.0
Pulmonary Disease	4.1