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Estimating the Effect of a Treatment When There Is Nonadherence in a Trial

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Randomized trials offer a powerful strategy for estimating the effect of a treatment on an outcome. However, interpretation of trial results can be complicated when study subjects do not take the treatment to which they were assigned; this is referred to as nonadherence. Prior authors have described instrumental variable approaches to analyze trial data with nonadherence; under their approaches, the initial assignment to treatment is used as an instrument. However, their approaches require the assumption that initial assignment to treatment has no direct effect on the outcome except via the actual treatment received (i.e., the exclusion restriction), which may be implausible. We propose an approach to identification of a causal effect of treatment in a trial with 1-sided nonadherence without assuming exclusion restriction. The proposed approach leverages the study subjects initially assigned to control status as an unexposed reference population; we then employ a bespoke instrumental variable analysis, where the key assumption is "partial exchangeability" of the association between a covariate and an outcome in the treatment and control arms. We provide a formal description of the conditions for identification of causal effects, illustrate the method using simulations, and provide an empirical application.

instrumental variables; nonadherence; noncompliance; randomized trials

Abbreviations: ATE, average treatment effect; BSIV, bespoke instrumental variable; CI, confidence interval; ITT, intention-to-treat; IV, instrumental variable; LATE, local average treatment effect.

Randomized experiments are powerful tools for understanding the causal effect of a treatment. However, complications can arise when study participants do not take the treatment assigned; this is referred to as nonadherence to (or noncompliance with) the assigned treatment (1). Concern arises when nonadherence is nonrandom, which it often is because nonadherent behavior typically is self-selected (i.e., a participant opts not to take the treatment as assigned). Such settings are common in randomized clinical trials, and consequently nonadherence is an important potential challenge to a causal interpretation of randomized trial results (2).

An intention-to-treat (ITT) analysis, in which we compare the risk of the outcome among persons assigned to receive treatment versus control participants, will entangle the effect of the treatment with the effect of nonadherence (3). An ITT analysis does yield a valid estimate of the effectiveness of the randomized assignment; however, it does not yield a valid estimate of the actual efficacy of the treatment, because the study includes subjects who have not adhered to the assigned treatment (4, 5).

An as-treated analysis, in which we compare persons who received treatment with those who did not, typically disregards the initial randomization. An as-treated analysis may yield a biased estimate of efficacy of the treatment because such an analysis is no longer afforded the expectation of unconfoundedness that is provided by randomization to treatment, even conditional on assigned treatment. Therefore, factors associated with receiving treatment may also be associated with the outcome and confound an as-treated analysis.

Prior authors have discussed approaches to analysis of trial data with nonadherence (4, 6–8). Instrumental variable (IV) approaches are among the most commonly used to assess treatment effects in settings of trials with nonadherence (9). For example, Robins (7) and Angrist et al. (10) have described IV approaches in which the random assignment

is used as an IV, unaffected by any unmeasured cause of the outcome and typically strongly predictive of the actual treatment received (7, 10). However, as in any IV setting, a causal interpretation requires the condition of "exclusion restriction," whereby the initial assignment to treatment has no effect on the outcome except through treatment (10, 11)—an assumption that often may be implausible in trial settings. Another widely used approach is based on fitting a structural model—for example, by applying inverse probability of censoring weights (12). A causal interpretation of the treatment effect under such approaches requires that nonadherence be ignorable conditional on the available measured covariates, which may be implausible when important potential confounders are not measured.

Here, we propose an alternative approach to estimation of causal effects in trial settings with nonadherence that does not require the exclusion restriction condition. Importantly, the conditions needed to identify a causal effect of treatment differ from those required by a standard IV approach (7, 10). Notably, our proposed approach requires neither a standard "exclusion restriction" assumption nor the assumption that nonadherence is ignorable conditional on measured covariates. Access to different approaches that leverage different identifying conditions may be useful for investigators who wish to triangulate evidence and conduct informative sensitivity analyses.

METHODS

Let R denote random assignment to control ($R = 0$) or treatment ($R = 1$) status. Let A be a binary indicator of actual treatment received, either "did not receive treatment" ($A = 0$) or "received treatment" ($A = 1$). Let Y be an outcome of interest measured at the end of the study, and let L denote measured covariates on which data are collected prior to treatment assignment (i.e., baseline characteristics). Adherence occurs when R equals A, and nonadherence occurs when R does not equal A. For simplicity, nonadherence is defined here as a binary variable at a single time point.

One-sided nonadherence

We focus on trial settings in which there is 1-sided nonadherence, such as that which arises when the control group is prohibited access to the treatment (i.e., if $R = 0$ then $A = 0$, by design). For example, the control group is constrained to receive the standard of care, while the treated group may (or may not) comply with treatment (13).

Population average treatment effect

Suppose that each person in the target population has a potential outcome variable Y^a that would be observed if, possibly contrary to fact, they were exposed to treatment value a. We might be interested in quantifying the population average treatment effect (ATE),

$$\text{ATE} = E\left[Y^{a=1} - Y^{a=0}\right],$$

as a causal measure of the efficacy of the treatment.

We can readily obtain the ITT estimator,

$$\text{ITT} = E[Y|R = 1] - E[Y|R = 0],$$

by a regression model for the outcome Y as a function of R. Under the optimal condition of full adherence with treatment assignment, the ITT estimator provides an estimate of the ATE,

$$\begin{aligned}\text{ITT} &= E[Y|R = 1, A = 1] - E[Y|R = 0, A = 0] \\ &= E[Y|R = 1] - E[Y|R = 0] \\ &= E[Y|A = 1] - E[Y|A = 0],\end{aligned}$$

where, assuming consistency, such that $Y = Y^a$ if $A = a$, we identify the ATE. However, if there is nonadherence, we need to distinguish between the effect of treatment assignment (R) and the effect of treatment adherence (A).

Approach of Angrist et al. In their 1996 article, Angrist et al. (10) described an IV approach to analysis of trial data with nonadherence, noting that R, the random assignment to treatment, may serve as an IV in an analysis that aims to estimate the effect of the actual treatment received, A. Their IV estimate may be obtained via a 2-stage regression as follows:

i. Obtain the predicted value of A given R, $\hat{A}(R) = \hat{E}(A|R)$. This is estimated via an ordinary least-squares regression of A on R in the trial data, yielding $\hat{A}(R)$ for each study participant.
ii. Fit a regression of Y on $\hat{A}(R)$ of the form $E(Y|\hat{A}(R)) = \alpha_0 + \alpha_1\hat{A}(R)$ to obtain the ordinary least-squares estimator $\hat{\alpha}_1$.

For this simple IV estimator to recover (i.e., be consistent for) the average causal effect of A on Y, 3 instrumental conditions are required:

1) instrument relevance (a nonnull association between R and A);
2) exclusion restriction: $Y^{r=1,a} = Y^{r=0,a}$, for $a = 0, 1$; and
3) marginal exchangeability: $Y^{r,a} \perp R$ for all a, r.

Under full adherence, the Angrist et al. (10) estimator of the ATE equals the ITT estimator, because under full adherence, $\hat{A}(R) = 1$ when $R = 1$, else 0. Given nonadherence, an additional condition (condition 4) must hold for causal identification: Angrist et al. (10) make a monotonicity assumption regarding absence of study participants who are defiers of their treatment assignment (i.e., $A^{r=1} \geq A^{r=0}$, which is true by design in a study with 1-sided nonadherence such that $A^{r=0} = 0$, denoting by A^r the value of A that would be observed if assigned to control or treatment value r).

Given monotonicity, the Angrist et al. (10) estimator, $\hat{\alpha}_1$, targets what is sometimes called the local average treatment effect (LATE), $E[Y^{a=1} - Y^{a=0}|A^{r=1} = 1, A^{r=0} = 0]$; this quantity is also known as the complier average causal effect, using the term "complier" to refer to persons who adhere to their initial assignment. Note that the approach of Angrist et al. (10) and that of Robins (7) coincide in settings

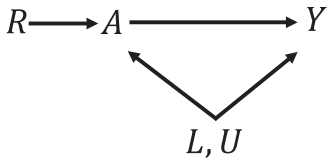

Figure 1. Relationship between treatment assignment (*R*), received treatment (*A*), an outcome (*Y*), a measured confounder (*L*), and an unmeasured confounder (*U*) in a setting of exclusion restriction.

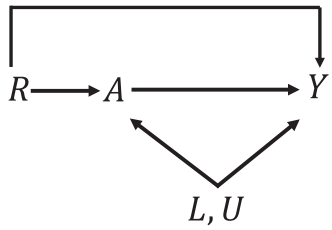

Figure 2. Relationship between treatment assignment (*R*), received treatment (*A*), an outcome (*Y*), a measured confounder (*L*), and an unmeasured confounder (*U*) in a setting that violates the exclusion restriction.

where there is 1-sided nonadherence, as does earlier work by Sommer and Zeger (14); the control group is prohibited access to the treatment, and therefore the LATE is equal to the effect of treatment on the treated randomized to treatment.

Figure 1 illustrates that although the *A*-*Y* association may be confounded by measured (*L*) or unmeasured (*U*) causes of nonadherence, *R* has the structural characteristics of an IV. Crucially, any effect of assignment to treatment on outcome *Y* operates only through its effect on *A*.

When the exclusion restriction does not hold. However, there are many settings, such as a trial in which double-blinding is not possible, where we may be concerned that the assumption of exclusion restriction does not hold. In Figure 2, random assignment to treatment (*R*) may directly affect *Y*, as well as affect *A*. *R* no longer has the structural characteristics of an IV; and an estimate of the effect of *A* on *Y* may be confounded by measured (*L*) or unmeasured (*U*) causes of nonadherence, as well as by *R*. We propose an approach to estimation of causal effects in this setting and show how to specifically distinguish between the effect of treatment assignment (*R*) and the effect of treatment adherence (*A*).

As a motivating example, consider a trial of the effect of a 2-dose vaccine in which, at baseline, trial participants receive either the first dose of vaccine or a placebo. We may assume effective double-blinding and full adherence to the first dose of vaccine or placebo (delivered at study enrollment). Subsequently, study subjects should return for a second dose of the vaccine or placebo. In this case, random assignment to treatment includes a first dose of the vaccine which may directly affect *Y*, beyond its effects through receiving a second dose (*A*). However, an estimate of the effect of the second dose of vaccine on *Y* may be confounded by hidden causes of nonadherence; and *R* no longer has the structural characteristics of an IV. Consequently, if we are interested in an estimate of the effect of the vaccine beyond just receiving a first dose (e.g., the effect of a second dose of vaccine on *Y*), then we may be concerned about an exclusion restriction violation (Figure 2). The vaccine trial example can be considered a special case of time-varying nonadherence, which is not necessarily problematic in the framework of Robins (7) but requires imposing additional parametric restrictions on the causal effects (which our approach does not require).

Our proposed approach. Although we propose an IV-type approach, under our proposed method randomization, *R*, is not used as an instrument. Rather, randomization is used to define a reference population that cannot access treatment at a later time postbaseline. Observations in the control arm of the trial provide information on covariate-outcome associations in a setting where the treatment is set to 0; we use that information to repurpose a measured covariate as a "bespoke instrumental variable" (BSIV), yielding a consistent estimator of the treatment effect in the treatment arm (15). Our proposed estimand may be obtained via a 3-step procedure as follows.

Step 1. Control arm of the study. We first focus on the study subjects initially assigned to the control arm of the study. Note that treatment exclusion is imposed, by design, in the control arm ($R = 0$) of a randomized trial with 1-sided nonadherence. The control arm serves as a reference population with no possible access to treatment (i.e., *A* is set to 0 for participants in the control arm). Using just the subjects in the control arm of the trial, we estimate the association between a measured covariate, *L*, that will subsequently serve as a BSIV, and the outcome, *Y*:

i. Obtain the predicted value of *Y* given *L* in the control arm of the trial, $\hat{F}(L) = \hat{E}(Y|L, R = 0)$. This is estimated by a regression of *Y* on *L* in the control arm ($R = 0$).

Step 2. Treated arm of the study. Next, we focus on the study subjects initially assigned to the treatment arm of the study ($R = 1$). The treatment arm of the trial serves as a study sample in which we propose to estimate the association between the covariate, *L*, and adherence. Using just the treatment arm of the trial, we estimate the association between a measured covariate, *L*, and the treatment received, *A*:

ii. Obtain the predicted value of *A* given *L* in the treatment arm of the trial, $\hat{A}(L) = \hat{E}(A|L, R = 1)$. This is estimated by a regression of *A* on *L* in the treatment arm ($R = 1$); we then evaluate $\hat{A}(L)$ for each study participant.

Step 3. Estimate the controlled direct effect of treatment assignment (*R*), if one were to set treatment, *A*, to its control value, among treated individuals assigned to treatment. Upon

evaluating $\hat{F}(L)$ and $\hat{A}(L)$ for all subjects initially assigned to the treatment arm, we can obtain our proposed estimates as follows:

iii. Fit a regression of Y on $\hat{A}(L)$ including $\hat{F}(L)$ as an offset,

$$E\left(Y|\hat{A}(L),\hat{F}(L),R=1\right)=\beta_0+\beta_1\hat{A}(L)+\hat{F}(L).$$

We recommend estimation using the generalized method of moments (16). Web Appendix 1 (available at https://doi.org/10.1093/aje/kwad141) provides a brief description of such an approach to estimation of the parameters of interest by a method of moments under an additive structural mean model (11, 17) and describes how to derive a bootstrap confidence interval (CI) for the estimate.

Sufficient conditions for identification of causal effects

Suppose that $L=(L_1, L_2)$ and that rather than taking all of L as candidate BSIVs, we take L_1 only as a BSIV and L_2 are additional covariates that we adjust for. Below we establish identification of the semiparametric structural nested model $E\left[Y^a-Y^{a=0}|a,l_2,R=1\right]=\beta\left(l_2\right)a$ leveraging the instrument-like properties of L_1.

Under the linear structural nested mean model defined above, given a trial in which subjects were randomized to R, with 1-sided nonadherence, we require the following conditions.

1. Consistency, such that $Y^a=Y$ if $A=a$ and $R=1$.

2. Bespoke instrument relevance, a nonnull association between L_1 and A, such that, given $l_1\neq 0$, $E\left[A|l_1,l_2,R=1\right]-E\left[A|l_1=0,l_2,R=1\right]\neq 0$ for each observed l_2.

3. Partial population exchangeability, such that

$$\begin{aligned}m\left(L_1,L_2\right)&=E\left[Y^{a=0}|R=0,L_1,L_2\right]\\&\quad-E\left[Y^{a=0}|R=0,L_1=0,L_2\right]\\&=E\left[Y^{a=0}|R=1,L_1,L_2\right]\\&\quad-E\left[Y^{a=0}|R=1,L_1=0,L_2\right].\end{aligned}$$

4. Partial additive causal effect homogeneity (i.e., no modification of the effect of A on Y by L_1 on the scale of interest) in causing the outcome, such that

$$\begin{aligned}&E[Y^a-Y^{a=0}|A=a,l_1,l_2,R=1]\\&\quad=E[Y^a-Y^{a=0}|A=a,l_1=0,l_2,R=1]\end{aligned}$$

for all l_1. Condition 1 is a standard consistency assumption. Condition 2 simply requires that the "bespoke" instrument, L_1, predicts treatment A; this can be empirically assessed, and the investigator is free to select among measured covariates to identify which variable(s) best satisfy this condition. Condition 3 essentially requires that the L_1-Y additive association (conditional on L_2) in the control arm of the trial equals the L_1-$Y^{a=0}$ additive association (conditional on L_2) in the treatment arm. An alternative interpretation of the assumption can be obtained given randomization of R, as $E\left[Y^{a=0,r=1}-Y^{a=0,r=0}|L_1=1,L_2\right]=E\left[Y^{a=0,r=1}-Y^{a=0,r=0}|L_1=0,L_2\right]$, which states that the additive effect of being randomized to the treatment arm versus the control arm (i.e., any violation of the exclusion restriction), fixing subsequent treatment at $A=0$, is constant across levels of L_1 conditional on L_2. Condition 4 is a homogeneity assumption which is not required but is sufficient for identification. Condition 4 clearly holds under the null hypothesis of no conditional effect of treatment in the treated, and therefore the proposed approach is guaranteed to produce a valid test of the null hypothesis of no additive treatment effect provided that the remaining conditions hold. We can exchange condition 4 for alternative assumptions—for example, by incorporating additional instruments in the model, thereby allowing additional degrees of freedom for identification of potential modification of the effect of A on Y by L_1.

Result: Under conditions 1–4, we have that $\beta\left(L_2\right)$ is identified by

$$\begin{aligned}&E\left[Y^{a=1}-Y^{a=0}|a=1,L_2,R=1\right]=\beta\left(L_2\right)\\&=\frac{\begin{array}{c}E\left[Y-m\left(L_1,L_2\right)|L,R=1\right]\\-E\left[Y-m\left(L_1,L_2\right)|L_1=0,L_2,R=1\right]\end{array}}{E\left[A|L,R=1\right]-E\left[A|L_1=0,L_2,R=1\right]},\end{aligned}$$

and the controlled direct causal effect of the randomized intervention if one were to set treatment, A, to its control value, is identified by

$$\begin{aligned}&E\left[Y^{a=0,r=1}-Y^{a=0,r=0}|L\right]=E\left[Y|R=1,L\right]\\&\quad-E\left[Y|R=0,L\right]-\beta\left(L_2\right)\Pr\left(A=1|L,R=1\right).\end{aligned}$$

A proof of the first part of the result can be obtained as a special case of the BSIV general identification result of Richardson and Tchetgen Tchetgen (15), in the special case where the mechanism of selection into what they define as target ($R=1$) and reference ($R=0$) populations is known by design (i.e., by randomization). Richardson and Tchetgen Tchetgen (15) also provide justification for a 2-stage least-squares estimator of $\beta\left(L_2\right)$, under linear models without interactions—that is, assuming that $E\left[Y^{a=1}-Y^{a=0}|a=1,L_2,R=1\right]=\beta\left(L_2\right)=\beta_1$ and $E\left[Y^{a=0}|L_2=l_2\right]=\beta_0+\beta_2 l_2$. A proof for the second part of the result is novel and is provided in Web Appendix 1.

Interpretation of the model

The estimated parameter $\hat{\beta}_1$ describes the effect of receiving treatment among persons who were assigned to treatment and took it, $E\left[Y^{a=1}-Y^{a=0}|R=1,A=1,l\right]$. In our motivating example, $\hat{\beta}_1$would describe the effect of receiving 2 doses of vaccine versus 1 dose, in the vaccine arm of the trial. Note that under the BSIV identifying conditions 1–4, $\hat{\beta}_1$ is not confounded by measured (L) or

unmeasured (U) factors. If the exclusion restriction holds, $\hat{\beta}_1$ can be interpreted as the LATE targeted by Angrist et al. (10), or as the effect of treatment on the treated assigned to treatment; if the exclusion restriction does not hold, $\hat{\beta}_1$ might be expected to differ from the estimand proposed by Angrist et al. (10), but it can still, under our identifying conditions, be interpreted as the effect of treatment on the treated assigned to treatment.

Furthermore, the estimated parameter $\hat{\beta}_0$ describes, under our conditions, the effect of assignment to treatment versus control (if subsequent treatment were fixed at 0), $E\left[Y^{r=1,a=0}|L=0\right] - E\left[Y^{r=0,a=0}|L=0\right]$. Therefore, $\hat{\beta}_0$ describes the direct effect (if one were to set treatment, A, to its control value) of assignment to treatment, R, rather than the total effect of R. In our motivating example, $\hat{\beta}_0$ would describe the effect of receiving 1 dose of vaccine versus nothing. If the exclusion restriction holds, then $\hat{\beta}_0$ equals 0; there is no direct effect of the assignment mechanism on the outcome.

As shown in Web Appendix 1, under our identification conditions, we can relate $\hat{\beta}_0$ and $\hat{\beta}_1$ to an estimate that one would obtain in an ITT analysis given full adherence, as follows:

$$\begin{aligned}\text{ITT} &= E\left[Y|R=1,l\right] - E\left[Y|R=0,l\right] \\ &= E\left[Y^{a_{r=1}=0,r=1} - Y^{r=0}|l\right] \\ &\quad + E\left[Y^{a} - Y^{a=0}|A=a,R=1,l\right] \times \Pr\left(A=1|l,r=1\right) \\ &= \beta_0 + \beta_1 \times \Pr\left(A=1|l,r=1\right).\end{aligned}$$

Therefore, when $\Pr\left(A=1|l,r=1\right)=1$, implying full adherence, $\widehat{\text{ITT}} = \hat{\beta}_0 + \hat{\beta}_1 = \widehat{\text{ATE}}$, as expected.

Simulation example. Data were simulated for 1,000 studies, with 5,000 people in each study. Each person was randomly assigned a covariate value L_1 by sampling from a uniform distribution, $L_1 \sim \text{Uniform}\,(-1, 1)$, a covariate value L_2 by sampling from a Bernoulli distribution, $L_2 \sim \text{Bern}(0.5)$, and treatment assignment value R by sampling from a Bernoulli distribution, $R \sim \text{Bern}(0.5)$. We allowed for 1-sided nonadherence by assigning A as a binary variable that took a value of 1 with probability $0.25 + 0.25L_1 + 0.25L_2$ for persons in the treatment arm ($R = 1$); in the control arm ($R = 0$), A was set to 0. Two outcome scenarios were explored. The first conformed to the "exclusion restriction" assumption, where the outcome variable, Y, was a continuous variable that took a value of $1 + 1 \times L_1 + 1 \times L_2 + 1 \times A + \varepsilon$, where $\varepsilon \sim N(0, 1)$. The second violated the "exclusion restriction" assumption, where the outcome variable, Y, was a continuous variable that took a value of $1 + 1 \times L_1 + 1 \times L_2 + 1 \times A + 1 \times R + \varepsilon$.

For each simulated data set, first we fitted an ITT model as a linear regression model for Y as a function of R. Second, we fitted the IV model approach of Angrist et al. (10); treatment assignment, R, was used as an IV in a 2-stage regression model for Y conditional on the expected value of A given R. Third, we estimated the proposed BSIV estimator using the approach described in the text (and the SAS code outlined in Web Appendix 2); we took L_1 as a BSIV. We summarized results from the simulated studies by computing the mean values of the estimated associations, the estimated standard deviations of the estimates (the empirical standard error), and the square root of the average squared differences between estimated associations and the specified true causal effects (the root mean squared error). Additional simulations were conducted that violated the assumption of additive effects (Web Appendix 3).

Empirical example. To illustrate the proposed method, we used data (March 2003–December 2005) from the Obstetrics and Periodontal Therapy Study, a randomized, blinded, controlled trial of nonsurgical periodontal treatment during pregnancy (18). Pregnant women aged 16 years or more who were at 13–16 weeks' gestation were recruited at Hennepin County Medical Center (Minneapolis, Minnesota), the University of Kentucky (Lexington, Kentucky), the University of Mississippi Medical Center (Jackson, Mississippi), and Harlem Hospital (New York, New York). Women were randomly assigned to receive either periodontal treatment or no intervention; women in the control arm were offered periodontal treatment after the end of the study. The treatment included: instruction in oral hygiene; scaling and root planing; and monthly tooth polishing (i.e., at 17–20, 21–24, 25–28, and 29–32 weeks' gestation). Persons in the control arm received only a brief oral examination. *Group* was a binary variable indicating whether the study participant was randomly assigned to the treatment or control arm. *Compliance* was a binary variable that took a value of 1 if treatment plans were completed by participants in the treatment group, else 0. The outcome of interest in our analysis, assessed at 29–32 weeks' gestation, was the fraction of gingival sites bleeding on probing at 29–32 weeks' gestation (V5%BOP), where higher values indicate more severe inflammation. Baseline covariates measured included a serum measure of fibrinogen level at baseline (OFIBRIN1) and serum endotoxin level at baseline (ETXU_CAT1); for the purposes of this illustrative example, a complete-case analysis was conducted restricted to those subjects with nonmissing values for the covariates and the outcome.

First, we fitted an ITT model as a linear regression model for V5%BOP as a function of group. Second, we fitted the IV model approach of Angrist et al. (10); treatment assignment, Group, was used as an IV in a 2-stage regression model for V5%BOP conditional on the expected value of Compliance given Group. Third, we estimated the proposed BSIV estimator using the approach described in the text; we utilized OFIBRIN1 and ETXU_CAT1 as BSIVs and used the SAS code shown in Web Appendix 2.

RESULTS

Simulation results

Under the first scenario, where the exclusion restriction holds, an ITT analysis yielded an average estimate of the effect of assignment to treatment, A, of 0.37 (Table 1); note that under the simulation setup, the probability of adherence conditional on assignment to treatment was 0.375. The IV

Table 1. Results From Simulations of the Association Between Treatment Assignment, Received Treatment, an Outcome, a Measured Confounder, and an Unmeasured Confounder[a]

Scenario and Model	Estimate	ESE (ASE)	RMSE
Scenario 1 (exclusion restriction holds)			
ITT	0.37	0.04 (0.04)	0.630
IV (LATE)	1.00	0.10 (0.10)	0.077
Proposed BSIV method			
$\hat{\beta}_0$[b]	0.00	0.07 (0.06)	0.062
$\hat{\beta}_1$[c]	1.00	0.20 (0.14)	0.158
$\hat{\beta}_0 + \hat{\beta}_1$[d]	1.00	0.12 (0.09)	0.102
Scenario 2 (exclusion restriction violated)			
ITT	1.37	0.04 (0.04)	0.373
IV (LATE)	3.66	0.11 (0.10)	2.663
Proposed BSIV method			
$\hat{\beta}_0$[b]	1.00	0.08 (0.06)	0.063
$\hat{\beta}_1$[c]	1.00	0.20 (0.14)	0.159
$\hat{\beta}_0 + \hat{\beta}_1$[d]	2.00	0.13 (0.09)	0.103

Abbreviations: ASE, average standard error; BSIV, bespoke instrumental variable; ESE, empirical standard error; ITT, intention to treat; IV, instrumental variable; LATE, local average treatment effect; RMSE, root mean squared error.

[a] 1,000 simulated cohorts with 5,000 observations in each cohort.

[b] Effect of treatment assignment.

[c] Effect of receiving treatment.

[d] The joint average treatment effect of being assigned to treatment and taking the treatment versus being assigned to the control arm (and therefore not having access to the treatment).

estimate based on the approach of Angrist et al. (10) was 1.00, conforming to the simulation setup (Table 1). Our proposed BSIV model yielded an average estimate of the effect of assignment to treatment versus placebo ($\hat{\beta}_0$) of 0.00, consistent with the simulation setup of the exclusion restriction; our proposed BSIV model yielded an average estimate of the effect of treatment A given assignment to treatment ($\hat{\beta}_1$) of 1.00, consistent with the simulation setup (Table 1); and our proposed BSIV model estimate of the average treatment effect, $\hat{\beta}_0 + \hat{\beta}_1 = 1.00$, also conformed to the simulation setup, albeit with a larger root mean squared error than the estimate based on the approach of Angrist et al. (10) or that of Robins (7).

Under the second scenario, where the exclusion restriction does not hold, an ITT analysis yielded an average estimate of the effect of assignment to treatment, A, of 1.37 (Table 1). The IV estimate based on the approach of Angrist et al. (10) was 3.66, not conforming to the simulation setup. Our proposed BSIV model yielded an average estimate of the effect of assignment to treatment versus placebo ($\hat{\beta}_0$) of 1.00, consistent with the simulation setup (Table 1); the proposed BSIV model yielded an average estimate of the effect of treatment A given assignment to treatment ($\hat{\beta}_1$) of 1.00, consistent with the simulation setup; and our proposed BSIV model estimate, $\hat{\beta}_0 + \hat{\beta}_1 = 2.00$, equaled the estimate one would obtain under an ITT analysis given full adherence under this simulation setup.

Web Appendix 3 shows additional simulations that violated the condition of "partial additive causal effect homogeneity" (condition 4). We first report simulations that conformed to the "exclusion restriction" assumption. An ITT analysis yielded an average estimate of the effect of assignment to treatment, A, of 0.46 (Web Table 1). The IV estimate based on the approach of Angrist et al. (10) was 1.22 (Web Table 1). The proposed BSIV model yielded biased estimates of the effect of assignment to treatment versus placebo and the effect of treatment when we (improperly) assumed effect homogeneity. Web Appendix 3 also shows additional simulations that violated both the conditions of "partial additive causal effect homogeneity" and "exclusion restriction." An ITT analysis yielded an average estimate of the effect of assignment to treatment, A, of 1.46. The IV estimate based on the approach of Angrist et al. (10) was 3.89. The proposed BSIV model yielded biased estimates of the effect of assignment to treatment versus placebo and the effect of treatment when we (improperly) assumed effect homogeneity. Web Appendix 3 also shows additional simulations in which the effect of A on Y varied with R. The IV estimate based on the approach of Angrist et al. (10) was 1.00, consistent with the effect of among the treated (Web Table 1). Our proposed BSIV model yielded an average

estimate of the effect of assignment to treatment versus placebo ($\hat{\beta}_0$) of 0.00, consistent with the simulation setup, and yielded an average estimate of the effect of treatment A given assignment to treatment ($\hat{\beta}_1$) of 1.00, consistent with the simulation setup (Web Table 1). The effect of treatment among persons not assigned to treatment is not identified in a study with 1-sided noncompliance.

Empirical results

The Obstetrics and Periodontal Therapy Study trial included 640 participants with nonmissing values for the covariates and outcome, of whom 314 were assigned to the treatment arm and 326 to the control arm. Of those in the treatment arm, 50% were nonadherent to the treatment. The ITT analysis yielded an estimated change in the percent fraction of gingival sites bleeding on probing of −0.24 (95% CI: −0.27, −0.21) among participants assigned to nonsurgical periodontal treatment (Table 2). The Angrist et al. (10) IV approach yielded an estimate of the effect of nonsurgical periodontal treatment on bleeding on probing of LATE = –0.48 (95% CI: −0.55, −0.42). The proposed BSIV approach yielded an average estimate of the effect of assignment to nonsurgical periodontal treatment versus control ($\hat{\beta}_0$) of −0.34 (95% CI: −0.44, −0.26), suggestive of violation of the "exclusion restriction" assumption (Table 2). The proposed BSIV model yielded an average estimate of the effect of nonsurgical periodontal treatment given assignment to treatment ($\hat{\beta}_1$) of 0.19 (95% CI: 0.05, 0.36); and the proposed BSIV model estimate of the joint average treatment effect of being assigned to treatment and taking the treatment versus being assigned to the control arm (and therefore not having access to the treatment) was $\hat{\beta}_0 + \hat{\beta}_1 = -0.14$ (95% CI: −0.22, −0.07), smaller in magnitude than the estimate obtained using the Angrist et al. (10) IV approach and somewhat less precise.

Table 2. Estimated Difference in the Fraction of Tooth Sites That Bled on Probing With Nonsurgical Periodontal Treatment, Obstetrics and Periodontal Therapy Study, March 2003–December 2005

Model	Estimate	95% CI
ITT	−0.24	−0.27, −0.21
IV	−0.48	−0.55, −0.42
Proposed BSIV method		
$\hat{\beta}_0$[a]	−0.34	−0.44, −0.26
$\hat{\beta}_1$[b]	0.19	0.05, 0.36
$\hat{\beta}_0 + \hat{\beta}_1$[c]	−0.14	−0.22, −0.07

Abbreviations: BSIV, bespoke instrumental variable; CI, confidence interval; ITT, intention to treat; IV, instrumental variable.
[a] Effect of treatment assignment.
[b] Effect of receiving treatment.
[c] The joint average treatment effect of being assigned to treatment and taking the treatment versus being assigned to the control arm (and therefore not having access to the treatment).

DISCUSSION

We propose a generalized IV approach to analysis of a randomized trial that suffers from 1-sided nonadherence. Using this approach, we can estimate the effect of the received treatment in comparison with persons who only experienced the effect of treatment assignment; and we also can estimate the joint average treatment effect of being assigned to treatment and taking the treatment versus being assigned to the control arm (and therefore not having access to the treatment).

Prior authors have described a variety of approaches to analysis of trial data with nonadherence. Some investigators advocate for simply reporting results of an ITT analysis in trials that suffer from nonadherence to treatment assignment (4). They argue that the ITT result provides a real-world estimate of the effect of prescribing a treatment protocol with which some patients will not comply. Robins (7) and Angrist et al. (10) described an IV approach that provides a simple powerful analysis of data, although requiring the strong assumption of exclusion restriction (10). Other approaches have been described as well, although they are less commonly used than ITT analysis and IVs (6–8, 19, 20). Imbens and Rubin (21) have proposed a Bayesian approach to imputation of compliance status, and Nagelkerke et al. (2) have proposed a regression model approach to adjustment for an indicator of the treatment received and the residuals from a regression of the treatment received on the treatment assigned. In the context of Mendelian randomization studies, an approach that is robust to violations of the exclusion restriction has been proposed, termed MR-GENIUS (22). The MR-GENIUS approach has different identifying conditions than our BSIV approach; notably, MR-GENIUS requires: 1) that candidate IVs (i.e., genetic variants) substantially affect the variance of the exposure under study; 2) that instruments do not interact on the additive scale with an unmeasured confounder in a regression model of the exposure on the instruments; and 3) that there is no interaction in the outcome structural model involving the exposure, the unmeasured confounder, and an instrument.

Our proposed approach not only does not require that we assume exclusion restriction, we estimate it and thereby provide a test of exclusion restriction under our identifying conditions. The availability of alternative approaches that can yield identification of causal effects under different identifying conditions can help investigators to triangulate evidence as well as conduct sensitivity analyses. We were motivated by consideration of a randomized trial of the effect of a vaccine in which, at baseline, study subjects receive either the first dose of vaccine or a placebo. Subsequently, the study subjects should return for a second dose of the vaccine or placebo, but some people do not return to receive the second dose. Nonadherence could pose a substantial challenge, and the exclusion restriction could require the implausible assumption that a first dose had no effect on the outcome except via the second dose of vaccine. In such a setting, under our proposed model, $\hat{\beta}_0$ corresponds to the effect of assignment to the treatment arm and receipt of a

single dose of vaccine versus being assigned to the control arm (and therefore not having access to the vaccine), and $\hat{\beta}_1$ corresponds to the effect of receiving both doses of vaccine versus a single dose. Under our identifying conditions, the sum, $\hat{\beta}_0 + \hat{\beta}_1$, corresponds to the joint average treatment effect of being assigned to treatment and taking the treatment versus being assigned to the control arm (and therefore not having access to the treatment); that estimate corresponds to the ITT result expected under full adherence. Although the structural nested modeling framework of Robins (7) can allow for general time-varying nonadherence if one wishes to infer the joint effects of time-varying treatments (7), this comes at the expense of additional parametric assumptions (e.g., that the effect of each treatment is the same). We have focused on estimation under an additive structural mean model. Future work may consider a multiplicative structural mean model, which may be preferable when the outcome mean can only take positive values.

Of course, if one assumes that the exclusion restriction holds and that a true IV is available, one can anchor study results at a standard IV estimate (7). Subsequently, one can leverage our proposed BSIV approach to validate the standard IV assumption of exclusion restriction. In fact, using our proposed approach, one can quantify the exclusion restriction assumption and assess whether the associated parameter, $\hat{\beta}_0$, is close to or equal to 0. Our proposed method also can help avoid problems of imprecision and bias that may arise in a standard IV analysis given a weak instrument (23) by allowing an investigator to leverage both the standard (true) IV and a strong "bespoke" instrument (or instruments) from among a set of measured covariates, Z (i.e., include the standard IV among the set L of covariates predicting treatment for our proposed approach).

In settings of partial adherence, as in our motivating example of a 2-arm blinded placebo-controlled trial of the efficacy of a 2-dose vaccine, one can estimate the effect of receiving the second dose of vaccine as compared with receiving only the first dose; and one also can estimate the total effect of being assigned to the treatment protocol and subsequently receiving both doses of vaccine (as compared with being assigned to placebo). We are not restricted to settings of partial adherence that involve just 2 time points. For example, under a 3-dose vaccine protocol, one could extend the approach (although it would require an additional BSIV). More generally, in settings of protracted treatments, nonadherence could be assessed at multiple time points, and our proposed method could be extended to such settings by additional BSIVs.

Nonadherence is a routine concern in randomized trials. We propose a novel approach to assessment of causal effects in trials with nonadherence. Rather than taking randomization to treatment as our IV and assuming that the exclusion restriction holds for this instrument, we leverage random assignment to a control arm as a means of generating a reference population in which treatment was set, by design, to 0. Using a novel BSIV approach, we exchange the standard exclusion restriction assumption for different identifying assumptions (that may be useful and plausible in many settings). The proposed approach offers a novel way to estimate efficacy and effectiveness of treatment effects in such settings.

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