Journal of the Royal Statistical Society
Statistical Methodology
Series B

J. R. Statist. Soc. B (2020)
82, *Part* 2, *pp.* 521–540

Multiply robust causal inference with double-negative control adjustment for categorical unmeasured confounding

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[Received March 2018. Final revision December 2019]

Summary. Unmeasured confounding is a threat to causal inference in observational studies. In recent years, the use of negative controls to mitigate unmeasured confounding has gained increasing recognition and popularity. Negative controls have a long-standing tradition in laboratory sciences and epidemiology to rule out non-causal explanations, although they have been used primarily for bias detection. Recently, Miao and colleagues have described sufficient conditions under which a pair of negative control exposure and outcome variables can be used to identify non-parametrically the average treatment effect (ATE) from observational data subject to uncontrolled confounding. We establish non-parametric identification of the ATE under weaker conditions in the case of categorical unmeasured confounding and negative control variables. We also provide a general semiparametric framework for obtaining inferences about the ATE while leveraging information about a possibly large number of measured covariates. In particular, we derive the semiparametric efficiency bound in the non-parametric model, and we propose multiply robust and locally efficient estimators when non-parametric estimation may not be feasible. We assess the finite sample performance of our methods in extensive simulation studies. Finally, we illustrate our methods with an application to the post-licensure surveillance of vaccine safety among children.

Keywords: Causal inference; Negative control; Semiparametric inference; Unmeasured confounding

1. Introduction

Causal inference in observational studies often relies on the assumption of no unmeasured confounding. However, as often happens in practice, when this assumption is violated, uncontrolled confounding can lead to biased estimates and invalid conclusions. Various methods have been proposed to detect and control for unmeasured confounding, among which the use of

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 1369–7412/20/82521

negative controls has recently gained increasing recognition and popularity. Negative controls have a long-standing tradition in laboratory sciences and epidemiology to rule out non-causal explanations of empirical findings (Rosenbaum, 1989; Weiss, 2002; Lipsitch *et al.*, 2010; Glass, 2014). Specifically, a negative control outcome is an outcome that is known not to be causally affected by the treatment of interest. Likewise, a negative control exposure is an exposure that does not causally affect the outcome of interest. To the extent possible, both negative control exposure and outcome variables should be selected such that they share a common confounding mechanism as the exposure and outcome variables of primary interest. For example, in a study about the effect of influenza vaccination on influenza hospitalization, injury or trauma hospitalization was considered a negative control outcome as it is not causally affected by influenza vaccination but may be subject to the same confounding mechanism mainly driven by health seeking behaviour (Jackson *et al.*, 2005). In this case, a non-null effect of the influenza vaccination against the negative control outcome amounts to compelling evidence of potential bias due to uncontrolled confounding. Another prominent example is the use of paternal exposure as a negative control exposure when determining the effect of maternal exposure during pregnancy on offspring health outcomes. Paternal exposure may have a similar association with the outcome to that of maternal exposure if there is hidden genetic or household level confounding (Davey Smith, 2008, 2012; Lipsitch *et al.*, 2012).

There is a growing literature on the use of negative controls to mitigate confounding bias. Rosenbaum (1992) considered testing and sensitivity analysis for unmeasured confounding by comparing matched treatment and control groups with respect to an unaffected outcome. Tchetgen Tchetgen (2013) developed an outcome calibration approach based on the idea that the counterfactual primary outcomes can stand as a proxy for unmeasured confounders and suffice to account for confounding of the exposure–negative control outcome association. Schuemie *et al.* (2014) proposed a p-value calibration approach by deriving an empirical null distribution of treatment effect by using a collection of negative controls. Sofer *et al.* (2016) generalized the difference-in-difference approach to the broader context of negative control outcome by allowing different scales for primary and negative control outcomes under a monotonicity assumption. In genetic studies, Gagnon-Bartsch and Speed (2012) and Wang *et al.* (2017) considered removing unwanted variation or batch effects by using negative control genes, which are assumed to be independent of the treatment of interest. In time series studies of air pollution, Flanders *et al.* (2011, 2017) considered partial correction of residual confounding by using a future exposure to air pollution as a negative control exposure. Miao and Tchetgen Tchetgen (2017) extended their method by incorporating both past and future exposures as multiple negative control exposures to attenuate confounding bias further.

The aforementioned methods rely on fairly restrictive assumptions such as rank preservation (Tchetgen Tchetgen, 2013), monotonicity (Sofer *et al.*, 2016) or linear models for the outcome and the unmeasured confounder (Gagnon-Bartsch and Speed, 2012; Wang *et al.*, 2017; Flanders *et al.*, 2011, 2017). Recently Miao *et al.* (2018) proposed non-parametric identification of causal effects by using a pair of negative control exposure and outcome variables under certain completeness conditions. Their work focused primarily on providing sufficient identification conditions and less so on inference. Ideally, one would in principle aim to obtain inferences in the non-parametric model under which causal effects are identifiable. However, in practice, because one may wish to account for a moderate to large number of observed confounders, non-parametric inference may not be feasible because of the curse of dimensionality.

In this paper, we propose to resolve this difficulty by developing a general semiparametric framework for inferences about the average treatment effect (ATE) in the context of categorical unmeasured confounding adjustment by using a pair of negative control exposure and outcome variables while accounting for a possibly large number of observed confounders. In particular, we first extend the identification result of Miao *et al.* (2018) to allow for a weaker set of conditions, and we provide an alternative representation of the identifying functional for the ATE. The representation is a difference between the standard g-formula of Robins (1986) that fails to account for unmeasured confounding and an explicit bias correction term that adjusts for unmeasured confounding bias leveraging a pair of negative controls. We then characterize three semiparametric estimators of the ATE that are consistent under three different semiparametric models. Each of the estimators operates on a subset of components of the likelihood for the observed data and therefore may be severely biased if the corresponding model is misspecified. We carefully combine these strategies into a multiply robust estimator that produces valid inference provided that one of three models is correct, without necessarily knowing which one is indeed correct (Robins *et al.*, 1994; Vansteelandt *et al.*, 2008; Tchetgen Tchetgen and Shpitser, 2012; Rotnitzky *et al.*, 2017). The multiply robust estimator operates on the union of the three semiparametric models and thus offers protection against model misspecification. Furthermore, our proposed multiply robust estimator is locally efficient in the sense that, when all working models are correctly specified, our estimator achieves the semiparametric efficiency bound for estimating the ATE under the union model.

The paper is organized as follows. In Section 2 we extend the non-parametric identification results of Miao *et al.* (2018) and provide an alternative representation of their identifying functional for the ATE, which opens up an opportunity for multiply robust estimation. For ease of exposition, we describe our results in the simple case of binary negative controls and unmeasured confounder in Section 3, where we propose a variety of semiparametric estimators including a multiply robust estimator. We extend our results to the more general setting of polytomous unmeasured confounding and negative controls in section C of the on-line supplementary material. In Section 4 we assess the finite sample performance of our proposed estimators via extensive simulations. We illustrate our methods with an application to the post-licensure surveillance of vaccine safety in Section 5. We close with a brief discussion in Section 6.

The vaccine safety surveillance data that are analysed in the paper are not publicly available because of privacy restrictions. The data may be obtained on request from the author for correspondence and with permission of the Vaccine Safety Datalink. The R code implementing the methods is available from `https://github.com/shixu0830/NegativeControlCategorical`.

2. Identification and reparameterization

We consider estimating the effect of a treatment A on an outcome Y subject to confounding by both observed covariates X and unobserved categorical variables U. Let $Y(a),\ a=0,1$, denote the counterfactual outcome that would be observed if the treatment were a. We are interested in the ATE defined as $E[Y(1)-Y(0)]$. Suppose that we observe also an auxiliary exposure variable Z and an auxiliary outcome variable W, and let $Y(a,z)$ and $W(a,z)$ denote the corresponding counterfactual values that would be observed if the primary treatment and auxiliary exposure had taken value (a,z). Then Z and W are the negative control exposure and negative control outcome respectively if they satisfy the following assumptions.

Assumption 1. Negative control exposure, $Y(a,z)=Y(a)$, for all z almost surely; negative control outcome, $W(a,z)=W$ for all a and z almost surely.

Fig. 1 presents a single-world intervention graph (Richardson and Robins, 2013) illustrat-

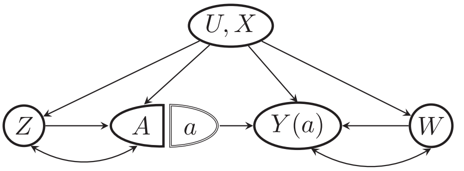

Fig. 1. Single-world intervention graph with unmeasured confounding U and double-negative control Z and W (Richardson and Robins, 2013): the bidirected arrow between Z and A (Y and W) indicates potential unmeasured common causes of Z and A (Y and W)

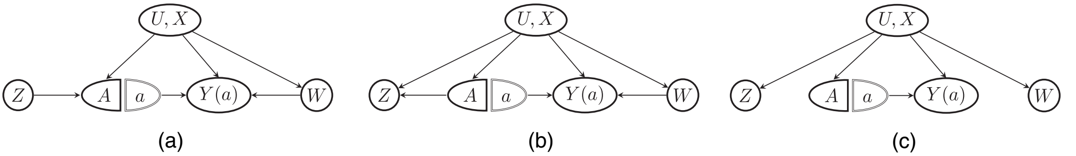

Fig. 2. Examples of alternative single-world intervention graphs: (a) Z is an instrumental variable (Miao *et al.*, 2019); (b) Z is a post-treatment variable that serves as a proxy of U; (c) Z and W are surrogates of U, and their roles can be switched; we have suppressed the bidirected arrow between Z and A (Y and W) because the common causes of Z and A (Y and W) do not confound the Y–A-relationship

ing an instance of the causal model under consideration. A key assumption that is satisfied by this graph is the conditional independence assumption stated below, which is required for identification of the causal effect.

Assumption 2. Latent ignorability: $(Z, A) \perp\!\!\!\perp (Y(a), W) | (U, X)$.

Assumption 2 states that U and X suffice to account for confounding of the relationship between (Z, A) and $(Y(a), W)$, whereas X alone may not. Moreover, U includes all unmeasured common causes of Z, A, Y and W except for that of the Z–A-association and Y–W-association. It is important to emphasize that Fig. 1 is not the only single-world intervention graph that satisfies the negative control assumptions. Fig. 2 presents examples of alternative graphs, all of which encode assumption 2. For example, a special case is when Z is an instrumental variable with the additional assumption that $Z \perp\!\!\!\perp U$, as shown in Fig. 2(a) (Miao *et al.*, 2019). Alternatively Z can be a post-treatment variable that serves as a proxy of U, as shown in Fig. 2(b). Furthermore, Fig. 2(c) presents a scenario where Z and W can be surrogates of U that satisfy the additional assumption that $(Z, W) \perp\!\!\!\perp (A, Y) | (U, X)$, which is the non-differential error assumption (Kuroki and Pearl, 2014). In this scenario, the roles of Z and W can be switched.

Remark 1. In practice, specification of the unmeasured confounder is helpful for justifying the validity of negative controls. In certain scenarios, however, we do not need to know what U is. For example, an underappreciated causal tenet is that the future does not affect the past. As such, with time series or longitudinal data, future exposure and past outcome may serve as negative exposure and outcome respectively, assuming no feedback effect from past outcome to future exposure. In this case, we can control for unmeasured confounders shared over time without singling out a specific U (Miao and Tchetgen Tchetgen, 2017).

Assumption 3. Consistency, $Y(a) = Y$ almost surely when $A = a$; positivity, $0 < P(A = a, Z = z \mid X) < 1$ for all a and z almost surely.

The consistency assumption ensures that the exposure is defined with enough specificity such that, among people with $A = a$, the observed outcome Y is a realization of the potential outcome value $Y(a)$. The positivity assumption states that in all observed covariate strata there are always some individuals with treatment and negative control exposure values ($A=a, Z=z$), for all a and z.

2.1. *Identification with categorical negative control variables*

In this paper, we consider the scenario where W, Z and U are categorical. Suppose that W, Z and U take $|W|$, $|Z|$ and $|U|$ possible values denoted w_i, z_j and u_s, for $i=0, \ldots, |W|-1$, $j=0, \ldots, |Z|-1$ and $s=0, \ldots, |U|-1$ respectively, where '$|\cdot|$' denotes the cardinality of a categorical variable. Let $P(\mathbf{W} \mid \mathbf{Z}, a, x)$ denote a $|W| \times |Z|$ matrix with $P(\mathbf{W} \mid \mathbf{Z}, a, x)_{i,j} = P(W=w_{i-1} \mid Z=z_{j-1}, A=a, X=x)$, $P(\mathbf{W}|\mathbf{U}, x)$ a $|W| \times |U|$ matrix with $P(\mathbf{W} \mid \mathbf{U}, x)_{i,s} = P(W=w_{i-1} \mid U=u_{s-1}, X=x)$ and $P(\mathbf{U} \mid \mathbf{Z}, a, x)$ a $|U| \times |Z|$ matrix with $P(\mathbf{U} \mid \mathbf{Z}, a, x)_{s,j} = P(U=u_{s-1} \mid Z=z_{j-1}, A=a, X=x)$. Similarly, let $E[Y \mid \mathbf{Z}, a, x]$ denote a $1 \times |Z|$ vector with $E[Y \mid \mathbf{Z}, a, x]_j = E[Y \mid Z=z_{j-1}, A=a, X=x]$, $E[Y \mid \mathbf{U}, a, x]$ a $1 \times |U|$ vector with $E[Y \mid \mathbf{U}, a, x]_s = E[Y \mid U=u_{s-1}, A=a, X=x]$ and $P(\mathbf{W} \mid x)$ a $|W| \times 1$ vector with $P(\mathbf{W} \mid x)_i = P(W=w_{i-1} \mid X=x)$. The following assumption describes a sufficient condition under which the ATE is non-parametrically identified.

Assumption 4. Both Z and W have at least as many categories as U, i.e. $|Z| \geqslant |U|$ and $|W| \geqslant |U|$. Both $P(\mathbf{W}|\mathbf{U}, x)$ and $P(\mathbf{U}|\mathbf{Z}, a, x)$ are full rank with rank $|U|$ at all values of a and x.

Remark 2. Under assumption 4, $P(\mathbf{W}|\mathbf{Z}, a, x)$ has rank $|U|$, which is proved in section A of the on-line supplementary material. Therefore, we can infer $|U|$ from the rank of $P(\mathbf{W}|\mathbf{Z}, a, x)$ (Choi *et al.*, 2017).

Assumption 4 imposes requirements on candidate negative controls for identification. Intuitively, both Z and W serve as proxies of U. Therefore, they should have at least as many possible values as U. They should also be strongly associated with U such that variation in U can be recovered from variation in Z and W. This is reflected by the requirement that the columns of $P(\mathbf{W}|\mathbf{U}, x)$ and the rows of $P(\mathbf{U}|\mathbf{Z}, a, x)$ must be linearly independent vectors. In practice, it is recommended to collect a negative control variable with a rich set of possible levels, or multiple negative control variables that can be combined into a composite negative control with as many categories as possible. However, selection of valid negative control variables must be based on reliable subject matter knowledge because assumptions 1–4 must be met.

The following lemma demonstrates identification of $E[Y(a)]$, which is proved in section A of the on-line supplementary material.

Lemma 1. Under assumptions 1–4, there is a $1 \times |W|$ vector $h(a, x)$ such that

$$E[Y|\mathbf{Z}, a, x] = h(a, x) P(\mathbf{W}|\mathbf{Z}, a, x), \tag{1}$$

and $E[Y(a)]$ is non-parametrically identified by $E[Y(a)] = \int_{\mathcal{X}} h(a, x) P(\mathbf{W}|x) f(x) \mathrm{d}x$, where $f(x)$ denotes the density function of X. Therefore, the ATE, denoted Δ, is uniquely identified by

$$\Delta = \int_{\mathcal{X}} \{h(1, x) - h(0, x)\} P(\mathbf{W}|x) f(x) \mathrm{d}x. \tag{2}$$

As stated in remark 2, $P(\mathbf{W}|\mathbf{Z}, a, x)$ has rank $|U|$ under assumption 4. When $|Z| = |W| = |U|$, $P(\mathbf{W}|\mathbf{Z}, a, x)$ is full rank and the linear system (1) has a unique solution

$$h(a, x) = E[Y|\mathbf{Z}, a, x] P(\mathbf{W}|\mathbf{Z}, a, x)^{-1}. \tag{3}$$

Therefore, lemma 1 implies the identification result of Miao *et al.* (2018) under the stronger assumption that $|Z| = |W| = |U|$, which is stated in the following corollary.

Assumption 5. Completeness: $P(\mathbf{W}|\mathbf{Z}, a, x)$ is invertible with $|Z| = |W| = |U| = k+1$, $k \geqslant 0$.

Corollary 1. Under assumptions 1–3 and 5, $E[Y(a)]$ is non-parametrically identified by

$$E[Y(a)] = \int_{\mathcal{X}} E[Y|\mathbf{Z}, a, x] P(\mathbf{W}|\mathbf{Z}, a, x)^{-1} P(\mathbf{W}|x) f(x) \mathrm{d}x.$$

Therefore, the ATE is given by

$$\Delta = \int_{\mathcal{X}} E[Y|\mathbf{Z}, A=1, X=x] P(\mathbf{W}|\mathbf{Z}, A=1, X=x)^{-1} P(\mathbf{W}|X=x) f(x) \mathrm{d}x \\ - \int_{\mathcal{X}} E[Y|\mathbf{Z}, A=0, X=x] P(\mathbf{W}|\mathbf{Z}, A=0, X=x)^{-1} P(\mathbf{W}|X=x) f(x) \mathrm{d}x. \quad (4)$$

When $|Z| > |U|$ or $|W| > |U|$, $P(\mathbf{W}|\mathbf{Z}, a, x)$ is rank deficient with linearly dependent rows or columns. In this case, there are infinite solutions to the linear system (1). Nevertheless, $E[Y(a)]$ remains uniquely identified. Note that there is always an invertible $|U| \times |U|$ submatrix of $P(\mathbf{W}|\mathbf{Z}, a, x)$ formed by deleting $|W| - |U|$ rows or $|Z| - |U|$ columns of $P(\mathbf{W}|\mathbf{Z}, a, x)$ (Gómez *et al.*, 2008). The $|W| - |U|$ rows or $|Z| - |U|$ columns correspond to free levels in W or Z that are redundant for identification but may improve efficiency.

We propose two strategies for estimation of Δ when $|Z| > |U|$ or $|W| > |U|$. One is to obtain a maximum likelihood estimator of $P(\mathbf{W}|\mathbf{Z}, a, x)$ and its Moore–Penrose inverse denoted as $P(\mathbf{W}|\mathbf{Z}, a, x)^{+}$. A particular solution to equation (1) is given by $h(a, x) = E[Y|\mathbf{Z}, a, x] P(\mathbf{W}|\mathbf{Z}, a, x)^{+}$. In fact, by theorem 2 of James (1978), the complete set of solutions to equation (1) is given by $h(a, x) = E[Y|\mathbf{Z}, a, x] P(\mathbf{W}|\mathbf{Z}, a, x)^{+} + \tau(a, x)^{\mathrm{T}} \{\mathbb{I} - P(\mathbf{W}|\mathbf{Z}, a, x) P(\mathbf{W}|\mathbf{Z}, a, x)^{+}\}$, as $\tau(a, x)$, a vector function, varies over all possible values in $\{f : (a, x) \to R^{|W|}\}$. The second is to coarsen levels in Z and W until the coarsened variables satisfy assumption 5 (Kuroki and Pearl, 2014; Miao *et al.*, 2018). Suppose that there are m possible sets of coarsened negative control variables; then an estimator can be obtained by the generalized method of moments, i.e. $\hat{\Delta} = \arg\min_{\Delta} (\mathbb{P}_n \hat{g}(\Delta))^{\mathrm{T}} \hat{W} (\mathbb{P}_n \hat{g}(\Delta))$, where $\hat{g}(\Delta)$ is an m-vector with each entry an estimating equation based on an estimated influence function of Δ under a given parametric, semiparametric or non-parametric model for a given set of coarsened negative control variables, and $\hat{W} = \mathbb{P}_n \{\hat{g}(\Delta) \hat{g}(\Delta)^{\mathrm{T}}\}^{-1}$. Such influence functions are derived in Section 3.

2.2. *Reparameterization of Δ for multiply robust estimation*

In this section, we provide an alternative parameterization of Δ which opens up an opportunity for multiply robust estimation in the case where $|Z| = |W| = |U| = k+1$. When $|Z| > |U|$ or $|W| > |U|$, to leverage the reparameterization, we use the second strategy described in Section 2.1, with $g(\Delta)$ being the efficient influence function (EIF) detailed in theorem 1 of Section 3.2.

2.2.1. *Motivation for multiply robust estimation*

As discussed in Section 1, non-parametric estimation of Δ may not be feasible when X is high dimensional or when Z and W have many levels, in which case we may need to resort to estimation under dimension reducing working models $E[Y|\mathbf{Z}, A, X; \theta_1]$, $P(\mathbf{W}|\mathbf{Z}, A, X; \theta_2)$ and $P(\mathbf{W}|X; \theta_3)$ where θ_1, θ_2 and θ_3 are finite dimensional, resolving the curse of dimensionality. Under such a specification of a model for the conditional distribution $P(Y, W, Z, A|X; \theta_1, \theta_2, \theta_3)$, one could in principle estimate Δ by using the plug-in estimator, which entails estimating θ_1, θ_2 and θ_3 by standard maximum likelihood estimation and substituting estimated parameters in equation (2) or (4), with the cumulative distribution function of X estimated by the empirical distribution. This is essentially the approach that was suggested by Miao *et al.* (2018). However, these working models are not in themselves of scientific interest and may be prone to model misspecification. The plug-in estimator may be severely biased if any of the three models is incorrect.

To resolve this difficulty, we develop a robust inferential approach grounded in semiparametric theory (Bickel *et al.*, 1993; Newey, 1990; Van der Vaart, 1998), detailed in Section 3. Specifically, we consider the task of estimating the functional Δ without any restriction on the observed data distribution, i.e. estimation in the non-parametric model denoted as $\mathcal{M}_{\text{nonpar}}$. We characterize the EIF for Δ in $\mathcal{M}_{\text{nonpar}}$. We then take the EIF as an estimating equation to obtain an estimator of Δ. Similarly to the plug-in estimator, EIF-based estimation entails estimating the distribution of the observed data under such a working model. However, unlike the plug-in estimator, we establish that our EIF-based estimator of Δ remains consistent and asymptotically normal (CAN) even when the observed data likelihood is partially misspecified. In fact, we establish the multiply robust property of our proposed estimator: it remains CAN under the union of three large semiparametric models, each of which restricts a subset of components of the likelihood, allowing the remaining likelihood components to be unrestricted and hence robust to misspecification.

2.2.2. *Reparameterization and intuition for identification*

An essential step towards constructing our multiply robust estimator involves a careful reparameterization of the functional Δ in terms of variation-independent components of the likelihood, such that (mis)specification of one particular component does not impose any restriction on the other components. To this end, we define the following contrasts measuring the observed effects of Z on Y and W at any value (a, x) as

$$\xi_{z_j}^{w_i}(a,x) = P(W = w_i | A = a, Z = z_j, X = x) - P(W = w_i | A = a, Z = z_0, X = x), \qquad i, j = 1, \ldots, k,$$
$$\xi_{z_j}^{Y}(a,x) = E[Y | A = a, Z = z_j, X = x] - E[Y | A = a, Z = z_0, X = x], \qquad j = 1, \ldots, k,$$

respectively, where z_0 is a user-specified reference level for Z. Likewise, the observed effects of A on Y and W at any values (z, x) are

$$\delta_A^{w_i}(z,x) = P(W = w_i | A = 1, Z = z, X = x) - P(W = w_i | A = 0, Z = z, X = x), \qquad i = 1, \ldots, k,$$
$$\delta_A^{Y}(z,x) = E[Y | A = 1, Z = z, X = x] - E[Y | A = 0, Z = z, X = x]$$

respectively. In addition, we let

$$\boldsymbol{\delta}_A^W(z,x) = (\delta_A^{w_1}(z,x), \delta_A^{w_2}(z,x), \ldots, \delta_A^{w_k}(z,x))^{\mathrm{T}}$$

denote a $k \times 1$ vector,

$$\boldsymbol{\xi}_Z^Y(a,x) = (\xi_{z_1}^Y(a,x), \xi_{z_2}^Y(a,x), \ldots, \xi_{z_k}^Y(a,x))^{\mathrm{T}}$$

denote a $k \times 1$ vector and $\boldsymbol{\xi}_Z^W(a,x)$ denote a $k \times k$ matrix with $\boldsymbol{\xi}_Z^W(a,x)_{i,j} = \xi_{z_j}^{w_i}(a,x), i, j = 1, \ldots, k$.

To avoid overparameterization, we omitted w_0 and z_0 in the contrasts, which are user-specified reference levels for W and Z respectively. The following lemma gives our alternative representation, which we prove in section B of the on-line supplementary material.

Lemma 2. Under assumptions 1–3 and 5, $\boldsymbol{\xi}_Z^W(a,x)$ is invertible and Δ in equation (4) admits the alternative representation

$$\left.\begin{aligned} \Delta &= \Delta_{\text{confounded}} - \Delta_{\text{bias}}, \\ \Delta_{\text{confounded}} &= E[\delta_A^Y(Z,X)], \\ \Delta_{\text{bias}} &= E[\mathbf{R}(1-A,X)\boldsymbol{\delta}_A^W(Z,X)], \end{aligned}\right\} \tag{5}$$

where $\mathbf{R}(a,x) = \boldsymbol{\xi}_Z^Y(a,x)^{\mathrm{T}} \boldsymbol{\xi}_Z^W(a,x)^{-1}$ is a $1 \times k$ vector. In addition, $\Delta_{\text{bias}} = 0$ if there is no unmeasured confounding.

The alternative representation illustrates the intuition behind identification of Δ. In expression (5), $\Delta_{\text{confounded}}$ is the standard g-formula which fails to adjust for unmeasured confounding, and Δ_{bias} is a bias correction term which accounts for unmeasured confounding. We note that Δ_{bias} is a scaled version of the observed association between A and W. In fact, by assumptions 1 and 2, $\boldsymbol{\delta}_A^W(Z,X)$ should be zero if there is no unmeasured confounding, and thus a non-zero $\boldsymbol{\delta}_A^W(Z,X)$ captures confounding bias. The scaling factor $\mathbf{R}(1-A,X)$ accounts for the fact that the effect of U on Y may not be on the same scale as the effect of U on W, and therefore the bias that is captured by $\boldsymbol{\delta}_A^W(Z,X)$ needs to be carefully rescaled. To identify the ratio of the effects of U on Y and U on W, we note that, conditionally on A and X, any association between Z and Y or Z and W is governed respectively by the effect of U on Y or U on W. Therefore the ratio of the observed Z-effects, i.e. $\mathbf{R}(1-A,X)$, recovers the ratio of the unobserved U-effects. We further illustrate the intuition behind identification and reparameterization with an example in section B.1 of the on-line supplementary material.

Decomposition of the causal effect estimand into the standard g-formula and an explicit bias correction term simplifies our inferential task, because semiparametric estimation of $\Delta_{\text{confounded}}$ has been extensively studied (Robins *et al.*, 1994; Robins, 2000; Scharfstein *et al.*, 1999; Van der Laan and Robins, 2003; Bang and Robins, 2005; Tan, 2006; Tsiatis, 2007). Therefore we mainly study robust estimation of Δ_{bias}, which together with $\Delta_{\text{confounded}}$ provides robust estimation of the ATE. For ease of exposition, in the following sections we develop our semiparametric approach in the setting where W, Z and U are binary variables. We extend our results to general settings with polytomous W, Z and U in section C of the on-line supplementary material.

3. Semiparametric estimation in the binary case

When Z, W and U are binary, i.e. $k=1$, $\boldsymbol{\delta}_A^W(z,x)$, $\boldsymbol{\xi}_Z^Y(a,x)$, $\boldsymbol{\xi}_Z^W(a,x)$ and $\mathbf{R}(a,x)$ simplify to the following scalar functions:

$$\left.\begin{aligned} \delta_A^W(z,x) &= E[W|A=1,Z=z,X=x]-E[W|A=0,Z=z,X=x],\\ \xi_Z^Y(a,x) &= E[Y|A=a,Z=1,X=x]-E[Y|A=a,Z=0,X=x],\\ \xi_Z^W(a,x) &= E[W|A=a,Z=1,X=x]-E[W|A=a,Z=0,X=x],\\ R(a,x) &= \xi_Z^Y(a,x)/\xi_Z^W(a,x), \end{aligned}\right\} \tag{6}$$

and representation of Δ in expression (5) is accordingly simplified. Note that careful specification of $R(A,X)$, $\xi_Z^W(A,X)$ and $\xi_Z^Y(A,X)$ is critical as they are in general not variation independent, i.e. model specification for $R(A,X)$ and $\xi_Z^W(A,X)$ would imply a model for $\xi_Z^Y(A,X)$.

3.1. Working models and three classes of semiparametric estimators

We now formally introduce variation-independent components of the observed data likelihood for estimation of Δ to facilitate robust estimation. First, we note that the mean of W given A, Z and X can be written as

$$E[W|A,Z,X]=E[W|A=0,Z=0,X]+\xi_Z^W(A=0,X)Z+\delta_A^W(Z=0,X)A+\eta_{AZ}^W(X)AZ, \tag{7}$$

where $\eta_{AZ}^W(\cdot)$ is the additive interaction of A and Z given X with

$$\eta_{AZ}^W(X)AZ=\{\xi_Z^W(A,X)-\xi_Z^W(A=0,X)\}Z=\{\delta_A^W(Z,X)-\delta_A^W(Z=0,X)\}A. \tag{8}$$

Furthermore, it is straightforward to verify that

$$E[Y|Z,A,X]=E[Y|Z=0,A,X]+R(A,X)\xi_Z^W(A,X)Z, \tag{9}$$

which implies that

$$\begin{aligned}\delta_A^Y(Z,X)=&E[Y|Z=0,A=1,X]+R(A=1,X)\xi_Z^W(A=1,X)Z\\ &-\{E[Y|Z=0,A=0,X]+R(A=0,X)\xi_Z^W(A=0,X)Z\}.\end{aligned} \tag{10}$$

Multiply robust estimation requires positing working models for the quantities $E[Y|Z=0,A,X]$, $E[W|A=0,Z=0,X]$, $\xi_Z^W(A=0,X)$, $\delta_A^W(Z=0,X)$, $\eta_{AZ}^W(X)$, $R(A,X)$ and $f(A,Z|X)$, where $f(A,Z|X)$ is the joint density of A and Z conditional on X. As X may be high dimensional and Z and W may have many levels, dimension reducing parametric (or semiparametric) working models are used to avoid the curse of dimensionality in practice. Clearly, these working models are not in themselves of scientific interest. Estimators relying on a subset of these models may be biased when the corresponding models are misspecified. To motivate and clarify our doubly robust estimator, we introduce three classes of semiparametric estimators of Δ, which are CAN under the following working models with finite dimensional indexing parameters.

(a) Model $\mathcal{M}_1$, working models $f(A,Z|X;\alpha^{A,Z})$ and $R(A,X;\beta^R)$ are correctly specified.
(b) Model $\mathcal{M}_2$, working models $f(A,Z|X;\alpha^{A,Z})$, and $\xi_Z^W(A,X;\beta^{WZ})$ and $\delta_A^W(Z,X;\beta^{WA})$ satisfying restriction (8) are correctly specified. The interaction model $\eta_{AZ}^W(X;\beta^{WAZ})$ is indexed by β^{WAZ}, which is a subvector shared by β^{WZ} and β^{WA}.
(c) Model $\mathcal{M}_3$, working models $R(A,X;\beta^R)$, and $E[Y|Z=0,A,X;\beta^Y]$ and $E[W|A,Z,X;\beta^W]$ with $\beta^W=(\beta^{W0},\beta^{WZ},\beta^{WA})$ are correctly specified, where $E[W|A,Z,X;\beta^W]$ is parameterized by equation (7) and β^{W0} denotes the subvector of β^W that indexes the baseline $E[W|A=0,Z=0,X]$.

Compared with the full list of variation-independent components, we can see that, in $\mathcal{M}_1$, $E[Y|Z=0,A,X]$, $E[W|A=0,Z=0,X]$, $\xi_Z^W(A=0,X)$, $\delta_A^W(Z=0,X)$ and $\eta_{AZ}^W(X)$ are unrestricted, in $\mathcal{M}_2$, $R(A,X)$, $E[Y|Z=0,A,X]$ and $E[W|A=0,Z=0,X]$ are unrestricted, whereas, in model $\mathcal{M}_3$, $f(A,Z|X)$ is unrestricted.

We now describe three semiparametric estimators which are CAN under models $\mathcal{M}_1$, $\mathcal{M}_2$ and $\mathcal{M}_3$. Let γ_i, $i=1,\ldots,3$, denote the collection of indexing parameters in the corresponding semiparametric working model $\mathcal{M}_i$, which can be estimated under $\mathcal{M}_i$ as detailed in Appendix A.1. Let $\hat{\gamma}_i$ denote the estimated parameters; we have

$$\hat{\Delta}_1=\mathbb{P}_n\left\{\frac{(2A-1)Y}{f(A|Z,X;\hat{\gamma}_1)}\right\}-\mathbb{P}_n\left\{E[R(1-A,X)|Z,X;\hat{\gamma}_1]\frac{(2A-1)W}{f(A|Z,X;\hat{\gamma}_1)}\right\},$$

$$\hat{\Delta}_2=\mathbb{P}_n\left\{\frac{(2A-1)Y}{f(A|Z,X;\hat{\gamma}_2)}\right\}-\mathbb{P}_n\left\{\frac{(2Z-1)Y}{f(Z|A,X;\hat{\gamma}_2)}\frac{E[\delta_A^W(Z,X)|1-A,X;\hat{\gamma}_2]}{\xi_Z^W(A,X;\hat{\gamma}_2)}\frac{f(1-A|X;\hat{\gamma}_2)}{f(A|X;\hat{\gamma}_2)}\right\},$$

$$\hat{\Delta}_3=\mathbb{P}_n\{E[Y|A=1,Z,X;\hat{\gamma}_3]-E[Y|A=0,Z,X;\hat{\gamma}_3]\}-\mathbb{P}_n\{R(1-A,X;\hat{\gamma}_3)\delta_A^W(Z,X;\hat{\gamma}_3)\},$$

where $\mathbb{P}_n$ is the empirical average operator, i.e. $\mathbb{P}_n(V)=(1/n)\Sigma_{i=1}^n V_i$.

Each of the three estimators above may be severely biased if their corresponding model $\mathcal{M}_1$, $\mathcal{M}_2$ or $\mathcal{M}_3$ is misspecified. For example, $\hat{\Delta}_1$ and $\hat{\Delta}_2$ will generally fail to be consistent if $f(A|Z,X)$ is misspecified, even if the rest of the components of the likelihood are correctly specified. Therefore, it is critical to develop a multiply robust estimator that remains CAN provided that one, but not necessarily more than one, of models $\mathcal{M}_1$, $\mathcal{M}_2$ and $\mathcal{M}_3$ is correctly specified, without necessarily knowing which one is indeed correct.

3.2. Efficient influence function in the non-parametric model

We aim to construct an estimator that is CAN under the union model $\mathcal{M}_{\text{union}} = \mathcal{M}_1 \cup \mathcal{M}_2 \cup \mathcal{M}_3$. For this, we first characterize the EIF for Δ in the non-parametric model $\mathcal{M}_{\text{nonpar}}$ which does not impose any restriction on the observed data distribution. We then use the EIF as an estimating equation and evaluate it under a working model to obtain an estimator of Δ. We establish multiple robustness and asymptotic normality of this estimator. We also provide a consistent estimator of the asymptotic variance for the estimators proposed.

It is well known that the EIF of $\Delta_{\text{confounded}}$ in $\mathcal{M}_{\text{nonpar}}$ (Robins *et al.*, 1994) is

$$\text{EIF}_{\Delta_{\text{confounded}}} = \frac{2A-1}{f(A|Z,X)}(Y - E[Y|A,Z,X]) + (E[Y|A=1,Z,X] - E[Y|A=0,Z,X]) - \Delta_{\text{confounded}}. \tag{11}$$

In theorem 1 below, we derive the EIF of Δ_{bias} in $\mathcal{M}_{\text{nonpar}}$, which is combined with $\text{EIF}_{\Delta_{\text{confounded}}}$ to obtain the EIF of Δ. Theorem 1 is proved in section D of the on-line supplementary material.

Theorem 1. Under assumptions 1–3 and 5, the EIF of the bias correction term Δ_{bias} in the non-parametric model $\mathcal{M}_{\text{nonpar}}$ is

$$\begin{aligned}\text{EIF}_{\Delta_{\text{bias}}} = {} & E[R(1-A,X)|Z,X]\frac{2A-1}{f(A|Z,X)}(W - E[W|A,Z,X]) \\ & + \frac{2Z-1}{f(Z|A,X)}(Y - E[Y|Z,A,X])\frac{E[\delta_A^W(Z,X)|1-A,X]}{\xi_Z^W(A,X)}\frac{f(1-A|X)}{f(A|X)} \\ & + R(1-A,X)\delta_A^W(Z,X) - \Delta_{\text{bias}}.\end{aligned}$$

The EIF of Δ is given by

$$\text{EIF}_\Delta(O) = \text{EIF}_{\Delta_{\text{confounded}}} - \text{EIF}_{\Delta_{\text{bias}}},$$

where $O = (Y, A, Z, W, Z)$ denotes the observed data. The semiparametric efficiency bound for estimating the ATE in $\mathcal{M}_{\text{nonpar}}$ is $E[\text{EIF}_\Delta(O)^2]^{-1}$.

Remark 3. Theorem 1 implies that, in $\mathcal{M}_{\text{nonpar}}$, all regular and asymptotically linear estimators $\hat{\Delta}$ are asymptotically equivalent and efficient with $\sqrt{n}(\hat{\Delta} - \Delta) = (1/\sqrt{n})\Sigma_{i=1}^n \text{EIF}_\Delta(O_i) + o_p(1)$ (Bickel *et al.*, 1993).

3.3. Multiply robust estimation of Δ

In this section, we consider the scenario where estimation under $\mathcal{M}_{\text{nonpar}}$ is not feasible because of potentially large numbers of measured covariates, and we proceed to estimation under $\mathcal{M}_{\text{union}}$. Specifically, we construct a multiply robust and locally efficient estimator of Δ by taking $\text{EIF}_\Delta(O)$ as an estimating equation and evaluating it under a working model for the observed data distribution to solve for Δ. Let

$$\theta = \{(\alpha^{A,Z})^{\text{T}}, (\beta^Y)^{\text{T}}, (\beta^{W0})^{\text{T}}, (\hat{\beta}^{WA})^{\text{T}}, (\hat{\beta}^{WZ})^{\text{T}}, (\hat{\beta}^R)^{\text{T}}\}^{\text{T}}$$

denote the nuisance parameters of the working models in $\mathcal{M}_{\text{union}}$. We estimate θ as the solution of the following collection of estimating equations.

First, we define the following score functions for maximum likelihood estimation of $f(A,Z|X;\alpha^{A,Z})$, $E[Y|A,Z=0,X;\beta^Y]$ and $E[W|A=0,Z=0,X;\beta^{W0}]$:

$$U_{\alpha^{A,Z}} = \frac{\partial}{\partial \alpha^{A,Z}} \log\{f(A, Z|X; \alpha^{A,Z})\},$$

$$U_{\beta^Y} = \frac{\partial}{\partial \beta^Y} \mathbb{1}(Z=0) \log\{f(Y|A, Z=0, X; \beta^Y)\},$$

$$U_{\beta^{W0}} = \frac{\partial}{\partial \beta^{W0}} \mathbb{1}(A=0, Z=0) \log\{f(W|A=0, Z=0, X; \beta^{W0})\},$$

where $f(A, Z|X; \alpha^{A,Z})$ is the conditional likelihood of (A, Z), $f(Y|A, Z=0, X; \beta^Y)$ is the conditional likelihood of Y restricted to the subsample with $Z=0$ and $f(W|A=0, Z=0, X; \beta^{W0})$ is the conditional likelihood of W restricted to the subsample with $A=0$ and $Z=0$.

Second, because $\delta_A^W(Z, X; \beta^{WA})$, $\xi_Z^W(A, X; \beta^{WZ})$ and $R(A, X; \beta^R)$ do not by themselves give rise to a likelihood function, we estimate them by constructing the following doubly robust g-estimation equations constructed under the union model $\mathcal{M}_{\text{union}}$:

$$U_{\beta^{WA},\beta^{WZ}} = (g_0(A, Z, X) - E[g_0(A, Z, X)|X; \alpha^{A,Z}])(W - E[W|A, Z, X; \beta^{W0}, \beta^{WZ}, \beta^{WA}]),$$
$$U_{\beta^R;\beta^Y,\beta^{W0},\beta^{WA}} = (g_1(A, Z, X) - E[g_1(A, Z, X)|A, X; \alpha^{A,Z}])(Y - E[Y|Z, A, X; \beta^R, \beta^Y, \beta^{W0}, \beta^{WA}]),$$

where $g_0(A, Z, X)$ and $g_1(A, Z, X)$ are user-specified vector functions, $E[g_0(A, Z, X)|X; \alpha^{A,Z}]$ and $E[g_1(A, Z, X)|X; \alpha^{A,Z}]$ are evaluated under $f(A, Z|X; \alpha^{A,Z})$ and $E[W|A, Z, X; \beta^{W0}, \beta^{WZ}, \beta^{WA}]$ and $E[Y|Z, A, X; \beta^R, \beta^Y, \beta^{W0}, \beta^{WA}]$ are parameterized as in equations (7)–(10). Let $\dim(v)$ denote the length of a vector v. We require that $g_0(A, Z, X)$ is of dimension $\dim(\beta^{WA}) + \dim(\beta^{WZ}) - \dim(\beta^{WAZ})$, and $g_1(A, Z, X)$ is of dimension $\dim(\beta^R)$ to generate adequate numbers of estimating equations.

In summary, let

$$U_\theta(O; \theta) = (U^{\mathrm{T}}_{\alpha^{A,Z}}, U^{\mathrm{T}}_{\beta^Y}, U^{\mathrm{T}}_{\beta^{W0}}, U^{\mathrm{T}}_{\beta^{WA},\beta^{WZ}}, U^{\mathrm{T}}_{\beta^R})^{\mathrm{T}}$$

denote the collection of the above-defined estimating equations. We estimate θ by solving $\mathbb{P}_n\{U_\theta(\theta)\} = 0$, and we denoted the estimator as

$$\hat{\theta} = \{(\hat{\alpha}^{A,Z}_{\text{mle}})^{\mathrm{T}}, (\hat{\beta}^Y_{\text{mle}})^{\mathrm{T}}, (\hat{\beta}^{W0}_{\text{mle}})^{\mathrm{T}}, (\hat{\beta}^{WA}_{\text{dr}})^{\mathrm{T}}, (\hat{\beta}^{WZ}_{\text{dr}})^{\mathrm{T}}, (\hat{\beta}^R_{\text{dr}})^{\mathrm{T}}\}^{\mathrm{T}}.$$

In particular, $\hat{\beta}^{WA}_{\text{dr}}$ and $\hat{\beta}^{WZ}_{\text{dr}}$ are CAN under the union model $\mathcal{M}_2 \cup \mathcal{M}_3$, and $\hat{\beta}^R_{\text{dr}}$ is CAN under the union model $\mathcal{M}_1 \cup \mathcal{M}_3$ (Robins and Rotnitzky, 2001; Wang and Tchetgen Tchetgen, 2018), which is proved in section E of the on-line supplementary material. We obtain the estimated working models by plugging $\hat{\theta}$ into equations (7)–(10), which is detailed in Appendix A.2.

The proposed multiply robust estimator solves $\mathbb{P}_n\{\text{EIF}_\Delta(O; \Delta, \hat{\theta})\} = 0$, where $\text{EIF}_\Delta(O; \Delta, \hat{\theta})$ is equal to $\text{EIF}_\Delta(O)$ evaluated at $(\Delta, \hat{\theta})$, i.e. the multiply robust estimator is

$$\hat{\Delta}_{\text{mr}} = \hat{\Delta}_{\text{confounded,mr}} - \hat{\Delta}_{\text{bias,mr}}$$

where

$$\hat{\Delta}_{\text{confounded,mr}} = \mathbb{P}_n\left\{\frac{2A-1}{f(A|Z, X; \hat{\theta})}(Y - E[Y|A, Z, X; \hat{\theta}]) + (E[Y|A=1, Z, X; \hat{\theta}] - E[Y|A=0, Z, X; \hat{\theta}])\right\}$$

$$\hat{\Delta}_{\text{bias,mr}} = \mathbb{P}_n\left\{E[R(1-A, X)|Z, X; \hat{\theta}]\frac{2A-1}{f(A|Z, X; \hat{\theta})}(W - E[W|A, Z, X; \hat{\theta}])\right.$$

$$+\frac{2Z-1}{f(Z|A,X;\hat{\theta})}(Y-E[Y|A,Z,X;\hat{\theta}])\frac{E[\delta_A^W(Z,X)|1-A,X;\hat{\theta}]}{\xi_Z^W(A,X;\hat{\theta})}\frac{f(1-A|X;\hat{\theta})}{f(A|X;\hat{\theta})}$$
$$+R(1-A,X;\hat{\theta})\delta_A^W(Z,X;\hat{\theta})\bigg\}.$$

The multiply robust estimator combines three semiparametric estimation strategies to produce robust inference provided that one of three working models is correct, without necessarily knowing which one is indeed correct. This can be seen by the fact that each of the three semiparametric estimators $\hat{\Delta}_i$ can be obtained by setting the components unrestricted in $\mathcal{M}_i$ to 0 in the above multiply robust estimator. Specifically, $\hat{\Delta}_1$ can be obtained by setting $E[Y|Z=0,A,X]$, $E[W|A=0,Z=0,X]$, $\xi_Z^W(A=0,X)$, $\delta_A^W(Z=0,X)$ and $\eta_{AZ}^W(X)$ to 0, $\hat{\Delta}_2$ can be obtained by setting $E[Y|Z=0,A,X]$, $E[W|A=0,Z=0,X]$ and $R(A,X)$ to 0 and $\hat{\Delta}_3$ can be obtained by setting $1/f(A|Z,X)$ and $1/f(Z|A,X)$ to 0. In particular, the multiply robust estimator of $\Delta_{\text{bias}}=E[R(1-A,X)\delta_A^W(Z,X)]$ does not require correct specification of both $R(1-A,X)$ and $\delta_A^W(Z,X)$. In fact, we improve robustness by incorporating the propensity of both exposures such that, when $f(A,Z|X)$ is correctly specified, $\hat{\Delta}_{\text{bias,mr}}$ is consistent if either $R(1-A,X)$ or $\delta_A^W(Z,X)$ is correctly specified. Our proposed estimator is also locally efficient in the sense that, when all working models are correctly specified, $\hat{\Delta}_{\text{mr}}$ achieves the semiparametric efficiency bound for estimating Δ in $\mathcal{M}_{\text{union}}$. Theorem 2 below summarizes the multiply robust and locally efficient property of $\hat{\Delta}_{\text{mr}}$.

Theorem 2. Under assumptions 1–3 and 5 and standard regularity conditions stated in section E of the on-line supplementary material, $\sqrt{n}(\hat{\Delta}_{\text{mr}}-\Delta)$ is regular and asymptotically linear under $\mathcal{M}_{\text{union}}$ with influence function

$$\text{IF}_{\text{union}}(O;\Delta,\theta^*)=\text{EIF}_\Delta(O;\Delta,\theta^*)-\frac{\partial\text{EIF}_\Delta(O;\Delta,\theta)}{\partial\theta^{\text{T}}}\bigg|_{\theta^*}E\left[\frac{\partial U_\theta(O;\theta)}{\partial\theta^{\text{T}}}\bigg|_{\theta^*}\right]^{-1}U_\theta(O;\theta^*),$$

and thus $\sqrt{n}(\hat{\Delta}_{\text{mr}}-\Delta)\to_{\text{d}}N(0,\sigma_\Delta^2)$, where $\sigma_\Delta^2(\Delta,\theta^*)=E[\text{IF}_{\text{union}}(O;\Delta,\theta^*)^2]$ and θ^* denotes the probability limit of $\hat{\theta}$. Furthermore, $\hat{\Delta}_{\text{mr}}$ is locally semiparametric efficient in the sense that it achieves the semiparametric efficiency bound for Δ in $\mathcal{M}_{\text{union}}$ at the intersection submodel $\mathcal{M}_{\text{intersect}}=\mathcal{M}_1\cap\mathcal{M}_2\cap\mathcal{M}_3$ where $\mathcal{M}_1$, $\mathcal{M}_2$ and $\mathcal{M}_3$ are all correctly specified.

We prove theorem 2 in section E of the on-line supplementary material. The rationale behind multiple robustness is based on the following key observation. A multiply robust estimator is bound to exist if we can describe an unbiased estimating equation in each of the submodels that form the union model. It then suffices to show that the multiply robust estimating equation (i.e. the EIF) reduces to each estimating equation under the corresponding submodel of the union model, by setting components which are left unrestricted in the submodel to a singleton value. For inference on Δ, a consistent standard error estimator follows from standard M-estimation theory, which is detailed in section E.3 of the supplementary material. We implemented the standard error estimator in both simulation and application studies. Alternatively, the nonparametric bootstrap may be used in practice, which is justified by the asymptotic linearity of the estimator (Cheng and Huang, 2010).

4. Simulation study

We investigate the finite sample performance of the various estimators of the ATE described in Section 3. We simulate 4000 samples of size $n=2000$ under the following data-generating mechanism:

(a) $X=(X_1,\ldots,X_8,X_7X_8)$ where $X_j \sim^{\mathrm{IID}} N(0,1)$, $j=1,\ldots,8$;
(b) A is Bernoulli with $P(A=1|X)=\mathrm{expit}(-0.01+\alpha^{\mathrm{T}}X)$;
(c) Z is Bernoulli with $P(Z=1|A,X)=\mathrm{expit}(-0.01-0.2A+\alpha^{\mathrm{T}}X)$;
(d) U is Bernoulli with $E[U|Z,A,X]=0.4Z+0.4AZ$;
(e) W is Bernoulli with $E[W|U=0,X]=\mathrm{expit}(-1+\beta^{\mathrm{T}}X)$, $E[W|U=1,X]-E[W|U=0,X]=0.5$;
(f) Y is Bernoulli with $E[Y|A=0,U=0,X]=\mathrm{expit}(-1+\beta^{\mathrm{T}}X)$, $E[Y|A,U=1,X]-E[Y|A,U=0,X]=0.25A$ and $E[Y|A=1,U,X]-E[Y|A=0,U,X]=0.25U$,

where $\alpha=-10^{-2}(1,1,1,1,1,1,1,1,-20)$ and $\beta=-10^{-1}(1,1,1,1,1,1,1,1,1)$. These parameters are chosen to ensure that $\mathrm{Pr}(U=1|Z,A,X)$, $\mathrm{Pr}(W=1|U,X)$ and $\mathrm{Pr}(Y=1|U,X)$ are between 0 and 1. The above models imply that

(a) $\xi_Z^W(A,X)=0.2+0.2A$, $\delta_A^W(Z,X)=0.2Z$ and $E[W|Z=0,A=0,X]=\mathrm{expit}(-1+\beta^{\mathrm{T}}X)$,
(b) $\xi_Z^Y(A,X)=0.2A$, $\delta_A^Y(Z,X)=0.2Z$ and $E[Y|Z=0,A=0,X]=\mathrm{expit}(-1+\beta^{\mathrm{T}}X)$ and
(c) $R(A,X)=0.5A$.

We evaluate the performance of the following five estimators of the ATE: three semiparametric estimators $\hat{\Delta}_1$, $\hat{\Delta}_2$ and $\hat{\Delta}_3$, the plug-in estimator that was discussed in Section 2.2.1, which we refer to as the maximum likelihood estimator MLE hereafter, and the multiply robust estimator Δ_{mr}. The true ATE is 0.07 on the risk difference scale. We consider the following scenarios to investigate the effect of modelling error.

(a) All models are correctly specified.
(b) Models $\mathcal{M}_2$ and $\mathcal{M}_3$ are wrong: $E[W|A,Z,X]$ is misspecified by assuming that both $\xi_Z^W(A,X)$ and $\delta_A^W(Z,X)$ are constant.
(c) $\mathcal{M}_1$ and $\mathcal{M}_3$ are wrong: $R(A,X)$ is misspecified by assuming that $R(A,X)$ is a constant.
(d) $\mathcal{M}_1$ and $\mathcal{M}_2$ are wrong: $f(Z|A,X)$ is misspecified by omitting the interaction term X_7X_8.
(e) All models are wrong: $f(Z|A,X)$ and $E[Y|A,Z,X]$ are misspecified by omitting the interaction term X_7X_8.

Table 1 summarizes the operating characteristics of $\hat{\Delta}_1$, $\hat{\Delta}_2$, $\hat{\Delta}_3$, MLE and the multiply robust estimator Δ_{mr} under the above model misspecification scenarios. We evaluated these estimators in terms of mean bias (scaled by 10^3), variance (scaled by 10^3), bias calculated as the proportion of the true ATE, the mean-squared error MSE (scaled by 10^3) and coverage of 95% confidence intervals (CIs) based on direct standard error estimates. The performance of MLE is not shown when $R(A,X)$ or $f(Z|A,X)$ is misspecified because it does not require specification of $R(A,X)$ or $f(Z|A,X)$ and thus remains unchanged under such misspecifications. Our proposed multiply robust estimator remained stable with relatively small bias across all scenarios, although as expected it had slightly larger variability. The multiply robust estimator performs better when all models are misspecified than if $\mathcal{M}_2$ and $\mathcal{M}_3$ are misspecified, which may not be the general case in practice as the theory does not necessarily justify it. In contrast, MLE and the other three semiparametric estimators that rely on $\mathcal{M}_1$, $\mathcal{M}_2$ and $\mathcal{M}_3$ can be substantially biased when their corresponding model was misspecified. The 95% CI coverages were close to the nominal level with the correctly specified model which indicated that our proposed standard error estimation provided valid inference. These results confirmed our theoretical results in finite sample and demonstrated the advantages of the proposed multiply robust estimator.

5. Observational post-licensure vaccine safety surveillance

We apply our method to an observational vaccine safety study comparing the risk of medically attended fever, which is a common adverse event following vaccination, among children who

Table 1. Operating characteristics of estimators under various model misspecification scenarios†

Scenario	*Method*	*Bias* ($\times 10^3$)	*Variance* ($\times 10^3$)	*Proportion bias* (% *ATE*)	*MSE* ($\times 10^3$)	*95% CI coverage*
All models are correct	Δ_1	−0.46	0.45	−0.65	0.45	0.95
	Δ_2	−0.37	0.62	−0.53	0.62	0.95
	Δ_3	−0.06	0.14	−0.08	0.14	0.95
	MLE	−0.49	0.10	−0.70	0.10	0.95
	Δ_{mr}	−0.39	0.73	−0.55	0.73	0.95
$\mathcal{M}_1$ correct; $\mathcal{M}_2$ and $\mathcal{M}_3$ misspecified	Δ_2	−7.10	0.48	−10.08	0.53	0.94
	Δ_3	−7.10	0.14	−10.08	0.19	0.91
	MLE	−24.05	6.47	−34.15	7.04	0.91
	Δ_{mr}	2.54	0.49	3.61	0.49	0.95
$\mathcal{M}_2$ correct; $\mathcal{M}_1$ and $\mathcal{M}_3$ misspecified	Δ_1	−0.51	0.50	−0.73	0.50	0.94
	Δ_3	−5.04	0.60	−7.22	0.63	0.95
	Δ_{mr}	0.27	0.56	0.39	0.56	0.95
$\mathcal{M}_3$ correct; $\mathcal{M}_1$ and $\mathcal{M}_2$ misspecified	Δ_1	−0.25	0.45	−0.36	0.45	0.95
	Δ_2	−1.22	0.61	−1.75	0.61	0.95
	Δ_{mr}	−0.05	1.14	−0.08	1.14	0.95
All models are misspecified	Δ_1	−0.25	0.45	−0.36	0.45	0.95
	Δ_2	−1.22	0.61	−1.75	0.61	0.95
	Δ_3	−2.80	0.14	−4.01	0.15	0.94
	MLE	−2.15	0.10	−3.08	0.10	0.94
	Δ_{mr}	0.60	1.10	0.86	1.10	0.95

†We trimmed the 5% tail of the second scenario extreme value of the maximum likelihood estimates.

received the combination diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine 'DTaP-IPV-Hib' with children who received other DTaP-containing comparator vaccines (Nelson *et al.*, 2013). The study population consisted of children aged from 6 weeks to 2 years enrolled at Kaiser Permanente Washington from September 2008 to January 2011. Healthcare databases routinely captured information on demographics, immunizations and diagnosis of fever within a 5-day post-vaccination risk window based on the international classification of diseases, ninth revision, code ICD-9.

In the absence of randomization, causal inference methods can be applied to evaluate the adverse effect of DTaP-IPV-Hib vaccine. However, because such administrative data are not collected for research purposes, potential bias due to unmeasured confounding can undermine the validity of the causal conclusion. In particular, parents of infants may request separate injections or the combination vaccine because of unmeasured health seeking preference, and such health seeking behaviour may be associated with fever diagnosis. To explore the possibility of confounding due to health seeking behaviour, the study monitored the presence of injury or trauma ICD-9 800–904 and 910–959) and ringworm ICD-9 110) within 30 days post vaccination, which are not expected to be related to the vaccine–outcome pair of interest. In particular, injury or trauma is unlikely to be causally affected by DTaP-IPV-Hib vaccination but may be associated with parents' health seeking behaviour on behalf of their children. Similarly, ringworm is unlikely to be a cause of fever that occurs during the 5-day risk window but may also be associated with health seeking behaviour. Therefore, we take injury or trauma as a negative control outcome and ringworm as a negative control exposure to detect and account for potential unmeasured confounding. During the study, 27064 DTaP-IPV-Hib vaccinations were administered, among which 60 fevers (0.22%) were observed within the risk window. In contrast, 19677 comparator vaccines were administered with 46 fevers (0.23%) observed. There were 45 ringworm cases and

Table 2. Adverse effect of DTaP-IPV-Hib vaccine on fever among children†

Scenario	*Method*	$\hat{\Delta}$ *(95% CI)*	*Proportion bias (%)*	*p-value*	$\hat{\Delta}_{\text{confounded}}$ *(95% CI)*	$\hat{\Delta}_{\text{bias}}$ *(95% CI)*
All models are non-parametric	Δ_1	1.7 (−1.1, 4.5)	0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
	Δ_2	1.7 (−1.1, 4.5)	0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
	Δ_3	1.7 (−1.1, 4.5)	0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
	MLE	1.7 (−1.1, 4.5)	0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
	Δ_{mr}	1.7 (−1.1, 4.5)	0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
$\mathcal{M}_1$ is non-parametric; $\mathcal{M}_2$ and $\mathcal{M}_3$ are restricted	Δ_2	1.7 (−1.4, 4.8)	−0.3	0.3	0.5 (−0.5, 1.4)	−1.2 (−4.1, 1.6)
	Δ_3	0.5 (−0.5, 1.4)	−72.3	0.3	0.5 (−0.5, 1.4)	−0.0 (−0.3, 0.3)
	MLE	1.6 (−1.5, 4.7)	−5.6	0.3	0.5 (−0.5, 1.4)	−1.1 (−4.0, 1.7)
	Δ_{mr}	1.6 (−1.3, 4.5)	−5.2	0.3	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.5)
$\mathcal{M}_2$ is non-parametric; $\mathcal{M}_1$ and $\mathcal{M}_3$ are restricted	Δ_1	1.7 (−1.1, 4.4)	−3.1	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.7, 1.3)
	Δ_3	1.7 (−1.1, 4.4)	−3.1	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.7, 1.3)
	Δ_{mr}	1.7 (−1.1, 4.6)	1.6	0.2	0.5 (−0.5, 1.4)	−1.3 (−3.9, 1.3)
$\mathcal{M}_3$ is non-parametric; $\mathcal{M}_1$ and $\mathcal{M}_2$ are restricted	Δ_1	1.7 (−1.1, 4.5)	0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
	Δ_2	1.7 (−2.4, 5.7)	−2.4	0.4	0.5 (−0.5, 1.4)	−1.2 (−5.1, 2.7)
	Δ_{mr}	1.7 (−1.1, 4.5)	−0.0	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.8, 1.3)
All models are restricted	Δ_1	1.7 (−1.1, 4.4)	−3.1	0.2	0.5 (−0.5, 1.4)	−1.2 (−3.7, 1.3)
	Δ_2	1.7 (−1.4, 4.8)	−0.3	0.3	0.5 (−0.5, 1.4)	−1.2 (−4.1, 1.6)
	Δ_3	1.4 (−0.4, 3.2)	−19.7	0.1	0.5 (−0.5, 1.4)	−0.9 (−2.4, 0.6)
	MLE	1.6 (−1.5, 4.7)	−5.6	0.3	0.5 (−0.5, 1.4)	−1.1 (−4.0, 1.7)
	Δ_{mr}	1.7 (−1.2, 4.7)	0.6	0.2	0.5 (−0.5, 1.4)	−1.3 (−4.0, 1.5)

†All point estimates and 95% CIs are scaled by 10^3. Proportion bias is the bias calculated as the proportion of the ATE under the saturated model (non-parametric model) taken as the true value.

46 injury or trauma cases. Sex and age group at vaccination (less than 5 months or 5 months–2 years) were also recorded.

Because A, Z and X are all binary, non-parametric, estimation based on empirical frequencies is in fact feasible. This is done by fitting a saturated model for each component of the likelihood by including main effects and all possible interactions. For example, the negative control outcome model was specified as

$$\begin{aligned}E[W|A,Z,X_1,X_2] = {} & \alpha_0 + \alpha_A A + \alpha_Z Z + \alpha_{X_1} X_1 + \alpha_{X_2} X_2 + \alpha_{A:Z} AZ + \alpha_{A:X_1} AX_1 + \alpha_{Z:X_1} ZX_1 \\ & + \alpha_{A:X_2} AX_2 + \alpha_{Z:X_2} ZX_2 + \alpha_{X_1:X_2} X_1X_2 + \alpha_{A:Z:X_1} AZX_1 + \alpha_{A:Z:X_2} AZX_2 \\ & + \alpha_{A:X_1:X_2} AX_1X_2 + \alpha_{Z:X_1:X_2} ZX_1X_2 + \alpha_{A:Z:X_1:X_2} AZX_1X_2,\end{aligned}$$

where X_1 denotes age group and X_2 denotes sex. As stated in remark 3, under $\mathcal{M}_{\text{nonpar}}$ when all nuisance parameters were non-parametrically estimated, all methods should produce exactly the same point estimate and confidence interval. We thus took the non-parametric model as the true model to illustrate robustness to departure from the non-parametric model via model restrictions in the following scenarios.

(a) $\mathcal{M}_2$ and $\mathcal{M}_3$ are restricted: $E[W|A,Z,X]$ is fitted without age–sex interaction.
(b) $\mathcal{M}_1$ and $\mathcal{M}_3$ are restricted: $R(A,X)$ is fitted without age–sex interaction.
(c) $\mathcal{M}_1$ and $\mathcal{M}_2$ are restricted: $f(Z|A,X)$ is fitted without age–sex interaction.
(d) All are restricted: $E[W|A,Z,X]$ and $R(A,X)$ are fitted without age–sex interaction.

Table 2 lists for each method the point estimates (scaled by 10^3) of Δ, $\Delta_{\text{confounded}}$ and Δ_{bias} and their 95% CIs (scaled by 10^3), the bias evaluated as the proportion of the ATE model under the non-parametric model which is taken as the true value and the p-value from a Wald test of $H_0:\Delta=0$. Similarly to the original study, our results indicated a slightly elevated risk of fever among children who received DTaP-IPV-Hib vaccine relative to children who received other DTap-containing comparator vaccines, although the effect was not statistically significant. In addition, there was no evidence of unmeasured confounding as the CI for Δ_{bias} included zero. As expected, under $\mathcal{M}_{\text{nonpar}}$, all methods provided exactly the same point estimate and CI. Under model misspecification, i.e. deviation from the NP model via model restrictions, all methods produced a stable estimate of $\Delta_{\text{confounded}}$, whereas Δ_{bias} was estimated with larger bias. The multiply robust estimator had generally smaller bias than did the other methods, which indicated that multiply robust estimation provided protection against model misspecification. A *caveat* is that in practice, if the negative control exposure is rare, the positivity assumption in assumption 3 may be violated. A sensitivity analysis switching the negative control variables produced similar conclusions, which are presented in section I of the on-line supplementary material.

6. Final remarks

In this paper, we have developed a general semiparametric framework for causal inference in the presence of unmeasured confounding leveraging a pair of negative control exposure and outcome variables. Our method provides an alternative to more conventional methods such as instrumental variable methods. Particularly, negative controls are sometimes available when a valid instrumental variable may not be, in settings such as air pollution studies (Miao and Tchetgen Tchetgen, 2017), genetic research (Gagnon-Bartsch and Speed, 2012) and observational studies using routinely collected healthcare databases such as electronic health records and claims data (Schuemie *et al.*, 2014). In particular, as a majority of the variables in administrative healthcare data are documented by medical codes and thus are naturally categorical, we believe that our application study demonstrated the promising role of double-negative control for detection and control of confounding bias in observational studies using healthcare databases. Our paper also contributes to the literature on differential confounding misclassification since negative controls can also be viewed as mismeasured versions of the unobserved confounder (Kuroki and Pearl, 2014; Ogburn and VanderWeele, 2012; Miao *et al.*, 2018). Our findings have established a theoretical basis for future research on semiparametric estimation with negative control adjustment for continuous unmeasured confounding. Another open problem is the possibility of using modern machine learning for estimation of high dimensional nuisance parameters in the context of multiply robust estimation much in the spirit of Athey and Wager (2017), Chernozhukov *et al.* (2016) and Van der Laan and Rose (2011).

Acknowledgements

We thank the Associate Editor and two referees for their helpful comments. Research reported in this publication was supported by the Beijing Natural Science Foundation, China (award Z190001, to Wang Miao), the Key Laboratory of Mathematical Economics and Quantitative Finance (Peking University), Ministry of Education, China (to Wang Miao), the Vaccine Safety Datalink from the Centers for Disease Control and Prevention, 2017–2022 (award 200-2012-53421, to Jennifer Nelson) and the National Institutes of Health (award R01AI104459, to Eric Tchetgen Tchetgen). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Centers for Disease Control and Prevention.

Appendix A

A.1. Estimation under models $\mathcal{M}_1$–$\mathcal{M}_3$

Throughout we use $\dim(v)$ to denote the length of a vector v, such as $\dim(\beta^R)$.

A.1.1. Estimation under model $\mathcal{M}_1$

The first class of estimators involves models $f(A, Z|X; \alpha^{A,Z})$ and $R(A, X; \beta^R)$ under $\mathcal{M}_1$, with nuisance parameter $\gamma_1 = (\alpha^{A,Z}, \beta^R)$. Specifically, let $\hat{\alpha}^{A,Z}_{\text{mle}}$ denote the maximum likelihood estimator of $\alpha^{A,Z}$ and define

$$f(A|Z, X; \hat{\alpha}^{A,Z}_{\text{mle}}) = f(A, Z|X; \hat{\alpha}^{A,Z}_{\text{mle}}) / \sum_a f(A=a, Z|X; \hat{\alpha}^{A,Z}_{\text{mle}})$$

and

$$f(Z|A, X; \hat{\alpha}^{A,Z}_{\text{mle}}) = f(A, Z|X; \hat{\alpha}^{A,Z}_{\text{mle}}) / \sum_z f(A, Z=z|X; \hat{\alpha}^{A,Z}_{\text{mle}}).$$

Because $R(A, X; \beta^R)$ does not by itself give rise to a likelihood function, we obtain an estimator $\hat{\beta}^R_{\text{gest}}$ of β^R by solving the following g-estimation-type equation (Robins, 1994; Wang and Tchetgen Tchetgen, 2018):

$$\mathbb{P}_n\{(h_1(A, Z, X) - E[h_1(A, Z, X)|A, X; \hat{\alpha}^{A,Z}_{\text{mle}}])\{Y - W\, R(A, X; \hat{\beta}^R_{\text{gest}})\}\} = 0,$$

where $h_1(A, Z, X)$ is a vector of user-specified $\dim(\beta^R)$ functions of A, Z and X, and $E[h_1(A, Z, X)|A, X; \hat{\alpha}^{A,Z}_{\text{mle}}]$ is evaluated under $f(Z|A, X; \hat{\alpha}^{A,Z}_{\text{mle}})$. We then have $\hat{\Delta}_1 = \hat{\Delta}_{\text{confounded, ipw}} - \hat{\Delta}_{\text{bias, gest}}$, where

$$\hat{\Delta}_{\text{confounded, ipw}} = \mathbb{P}_n\left\{\frac{(2A-1)Y}{f(A|Z, X; \hat{\alpha}^{A,Z}_{\text{mle}})}\right\},$$

$$\hat{\Delta}_{\text{bias, gest}} = \mathbb{P}_n\left(E[R(1-A, X; \hat{\beta}^R_{\text{gest}})|Z, X; \hat{\alpha}^{A,Z}_{\text{mle}}]\frac{(2A-1)W}{f(A|Z, X; \hat{\alpha}^{A,Z}_{\text{mle}})}\right).$$

A.1.2. Estimation under model $\mathcal{M}_2$

The second class of estimators involves models $f(A, Z|X; \alpha^{A,Z})$, $\xi_Z^W(A, X; \beta^{WZ})$ and $\delta_A^W(Z, X; \beta^{WA})$ under model $\mathcal{M}_2$, with nuisance parameter $\gamma_2 = (\alpha^{A,Z}, \beta^{WZ}, \beta^{WA})$. Specifically, let $\hat{\beta}_{\text{ipw}}^{WZ}$ and $\hat{\beta}_{\text{ipw}}^{WA}$ solve the following g-estimating equation:

$$\mathbb{P}_n\{(h_2(A, Z, X) - E[h_2(A, Z, X)|X; \hat{\alpha}_{\text{mle}}^{A,Z}])\{W - \xi_Z^W(A=0, X; \hat{\beta}_{\text{ipw}}^{WZ})Z - \delta_A^W(Z=0, X; \hat{\beta}_{\text{ipw}}^{WA})A - \eta_{AZ}^W(X; \hat{\beta}_{\text{ipw}}^{WAZ})AZ\}\} = 0$$

where $h_2(A, Z, X)$ is a vector of user-specified functions with dimension $\dim(\beta^{WZ}) + \dim(\beta^{WA}) - \dim(\beta^{WAZ})$, and $E[h_2(A, Z, X)|X; \hat{\alpha}_{\text{mle}}^{A,Z}]$ is evaluated under $f(A, Z|X; \hat{\alpha}_{\text{mle}}^{A,Z})$. Then $\hat{\Delta}_2 = \hat{\Delta}_{\text{confounded, ipw}} - \hat{\Delta}_{\text{bias, ipw}}$, where

$$\hat{\Delta}_{\text{confounded, ipw}} = \mathbb{P}_n\left\{\frac{2A-1}{f(A|Z, X; \hat{\alpha}_{\text{mle}}^{A,Z})}Y\right\},$$

$$\hat{\Delta}_{\text{bias, ipw}} = \mathbb{P}_n\left(\frac{(2Z-1)Y}{f(Z|A, X; \hat{\alpha}_{\text{mle}}^{A,Z})}\frac{f(1-A|X; \hat{\alpha}_{\text{mle}}^{A,Z})}{f(A|X; \hat{\alpha}_{\text{mle}}^{A,Z})}\frac{E[\delta_A^W(Z, X; \hat{\beta}_{\text{ipw}}^{WA})|1-A, X; \hat{\alpha}_{\text{mle}}^{A,Z}]}{\xi_Z^W(A, X; \hat{\beta}_{\text{ipw}}^{WZ})}\right).$$

A.1.3. Estimation under model $\mathcal{M}_3$

The third class of estimators involves models $E[W|Z, A, X; \beta^W]$, $E[Y|Z=0, A, X; \beta^Y]$ and $R(A, X; \beta^R)$ under model $\mathcal{M}_3$, with nuisance parameter $\gamma_3 = (\beta^W, \beta^Y, \beta^R)$. Specifically, let $\hat{\beta}_{\text{mle}}^W = (\hat{\beta}_{\text{mle}}^{W0}, \hat{\beta}_{\text{mle}}^{WZ}, \hat{\beta}_{\text{mle}}^{WA})$ denote the maximum likelihood estimator of β^W, and $\hat{\beta}_{\text{mle}}^Y$ denote the restricted maximum likelihood estimator of β^Y, where the latter is obtained by maximizing the likelihood under the working model $E[Y|Z=0, A, X; \beta^Y]$ restricted to the subsample with $Z=0$. Let $\hat{\beta}_{\text{or}}^R$ solve the estimating equation

$$\mathbb{P}_n[h_3(A, Z, X)\{Y - E[Y|Z=0, A, X; \hat{\beta}_{\text{mle}}^Y] - R(A, X; \hat{\beta}_{\text{or}}^R)(W - E[W|Z=0, A, X; \hat{\beta}_{\text{mle}}^W])\}] = 0,$$

where $h_3(A, Z, X)$ is a non-zero vector function of dimension $\dim(\beta^R)$. We obtain $E[Y|Z, A, X; \hat{\beta}_{\text{mle}}^Y, \hat{\beta}_{\text{mle}}^W; \hat{\beta}_{\text{or}}^R]$ by equation (9) using $E[Y|Z=0, A, X; \hat{\beta}_{\text{mle}}^Y]$, $\xi_Z^W(A, X; \hat{\beta}_{\text{mle}}^W)$ and $R(A, X; \hat{\beta}_{\text{or}}^R)$. Combining the above estimators, we have $\hat{\Delta}_3 = \hat{\Delta}_{\text{confounded, or}} - \hat{\Delta}_{\text{bias, or}}$, where $\hat{\Delta}_{\text{confounded, or}} = \mathbb{P}_n(E[Y|A=1, Z, X; \hat{\beta}_{\text{mle}}^Y, \hat{\beta}_{\text{mle}}^W; \hat{\beta}_{\text{or}}^R] - E[Y|A=0, Z, X; \hat{\beta}_{\text{mle}}^Y, \hat{\beta}_{\text{mle}}^W; \hat{\beta}_{\text{or}}^R])$ and $\hat{\Delta}_{\text{bias, or}} = \mathbb{P}_n\{R(1-A, X; \hat{\beta}_{\text{or}}^R)\delta_A^W(Z, X; \hat{\beta}_{\text{mle}}^W)\}$.

A.2. Estimated working models for the multiply robust estimator

Following the variation-independent parameterization that is detailed in equations (7)–(10), we specify the estimated working models by plugging in the corresponding components in θ as follows: $f(A|Z, X; \hat{\theta}) = f(A, Z|X; \hat{\alpha}_{\text{mle}}^{A,Z})/\Sigma_a f(A=a, Z|X; \hat{\alpha}_{\text{mle}}^{A,Z})$, $f(A|X; \hat{\theta}) = \Sigma_z f(A, Z=z|X; \hat{\alpha}_{\text{mle}}^{A,Z})$, $f(Z|A, X; \hat{\theta}) = f(A, Z|X; \hat{\alpha}_{\text{mle}}^{A,Z})/\Sigma_z f(A, Z = z|X; \hat{\alpha}_{\text{mle}}^{A,Z})$, $E[Y|A = 0, Z, X; \hat{\theta}] = E[Y|Z = 0, A, X; \hat{\beta}_{\text{mle}}^Y] + R(A, X; \hat{\beta}_{\text{dr}}^R)\xi_Z^W(A, X; \hat{\beta}_{\text{dr}}^{WA})Z$, $E[Y|Z, A, X; \hat{\theta}] = E[Y|Z=0, A, X; \hat{\beta}_{\text{mle}}^Y] + R(A, X; \hat{\beta}_{\text{dr}}^R)\xi_Z^W(A, X; \hat{\beta}_{\text{dr}}^{WZ})$, $E[W|A, Z, X; \hat{\theta}] = E[W|A=0, Z=0, X; \beta_{\text{mle}}^{W0}] + \xi_Z^W(A=0, X; \beta_{\text{dr}}^{WZ})Z + \delta_A^W(Z=0, X; \beta_{\text{dr}}^{WA})A + \eta_{AZ}^W(X; \beta_{\text{dr}}^{WAZ})AZ$, $E[R(1-A, X)|Z, X; \hat{\theta}] = \Sigma_a R(1-a, X; \hat{\beta}_{\text{dr}}^R)f(A=a|Z, X; \hat{\alpha}_{\text{mle}}^{A,Z})$ and $E[\delta_A^W(Z, X)|1-A, X; \hat{\theta}] = \Sigma_z \delta_A^W(z, X; \hat{\beta}_{\text{dr}}^{WA})f(Z=z|1-A, X; \hat{\alpha}_{\text{mle}}^{A,Z})$. In addition, to simplify the notation, we let $R(A, X; \hat{\theta}) = R(A, X; \hat{\beta}_{\text{dr}}^R)$, $\delta_A^W(Z, X; \hat{\theta}) = \delta_A^W(Z, X; \hat{\beta}_{\text{dr}}^{WA})$ and $\xi_Z^W(A, X; \hat{\theta}) = \xi_Z^W(A, X; \hat{\beta}_{\text{dr}}^{WZ})$.

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Supporting information
Additional 'supporting information' may be found in the on-line version of this article:

'Supplementary materials for "Multiply robust causal inference with double negative control adjustment for categorical unmeasured confounding"'.