Using negative controls to identify causal effects with invalid instrumental variables

Oliver Dukes¹, David B. Richardson², Zachary Shahn³, James M. Robins⁴, and Eric J. Tchetgen Tchetgen⁵

¹Ghent University, Ghent, Belgium
²University of California Irvine, Irvine, CA, USA
³CUNY School of Public Health, New York, NY, USA
⁴Harvard T. H. Chan School of Public Health, Boston, MA, USA
⁵University of Pennsylvania, Philadelphia, PA, USA

Abstract

Many proposals for the identification of causal effects require an instrumental variable that satisfies strong, untestable unconfoundedness and exclusion restriction assumptions. In this paper, we show how one can potentially identify causal effects under violations of these assumptions by harnessing a negative control population or outcome. This strategy allows one to leverage sup-populations for whom the exposure is degenerate, and requires that the instrument-outcome association satisfies a certain parallel trend condition. We develop the semiparametric efficiency theory for a general instrumental variable model, and obtain a multiply robust, locally efficient estimator of the average treatment effect in the treated. The utility of the estimators is demonstrated in simulation studies and an analysis of the Life Span Study.

Key words: causal inference; unmeasured confounding; semiparametric theory.

1 Introduction

There is now a long tradition in causal inference of developing identification strategies that do not rely on a 'no unmeasured confounding' (or conditional exchangeability) type assumption. One of the most popular of these is the 'instrumental variable' approach. For validity, instrumental variable-based causal inference relies on having access to a variable that satisfies the three core instrumental variable conditions: IV.1 it is associated with the exposure (relevance); IV.2 it affects the outcome only via the exposure (exclusion restriction); and IV.3 it shares no unmeasured common causes with the outcome (unconfoundedness) (Hernán and Robins, 2006).

Unfortunately, in much applied work the three core instrumental variable conditions may be violated. Recently, Davies et al. (2017) and Danieli et al. (2022) have considered how one can assess violations of IV.2 and IV.3 using *negative controls* (Lipsitch et al., 2010; Sofer et al., 2016). For example, physician preference is a popular choice of instrument in pharmacoepidemiologic studies, where interest might be on the causal effect of a particular treatment for a given disease. A negative control *population* for the instrument could be constructed based on patients for whom it is known that the treatment has no effect. Under IV.2 and IV.3, in this population physician preference should not be associated with the outcome of interest at all; hence any association is indicative of a violation of the exclusion restriction and/or unconfoundedness. In this work, we will introduce a more general concept of a *reference population*, of which a negative control population is a special case.

Alternatively, a negative control *outcome* is a variable for which it is implausible that there can be a causal effect of the exposure. Under the core instrumental variable assumptions, the instrument would then not be associated with the negative control outcome. For example, one might choose a clinical outcome unlikely to be affected by the medication. There is an existing literature on using negative control outcomes as a means to detect and remove bias in an analysis based on confounding adjustment (Lipsitch et al., 2010; Sofer et al., 2016); however, they have been used less for assessing the instrumental variable assumptions. Davies et al. (2017) describe how negative control outcomes can be used to compare the plausibility of instrumental variable approaches with analyses that assume no unmeasured confounding; Sanderson et al. (2021) use these variables to check for violations of unconfoundedness due to population stratification in Mendelian Randomisation studies.

We go beyond falsification testing and propose conditions for identification and estimation of effects with an invalid instrument variable. Our results rely on a condition on the stability of the association between the instrument and outcome, which is closely related to the *parallel trends* assumption in the difference-in-difference literature. Intuitively, our assumption states that the instrument-outcome association due to violations of IV.2 and IV.3 in the naïve instrumental variable analysis must equal the instrument-outcome association in a reference population. If our assumption holds, the potential instrument does not necessarily have to satisfy the conditions IV.2 and IV.3, but still must be predictive of the exposure, therefore satisfying IV.1. A special feature of our framework, relative to other negative control strategies, is that it allows one to leverage sub-populations who were *not eligible* to be exposed. We hope that our methodology may be generally useful in epidemiologic applications where such sub-populations arise.

In this paper, we first formalise conditions for identification of the average treatment effect on the treated given a potentially invalid instrument and negative control/reference population. These results hold interesting connections with recent work on instrumental variables, difference-in-differences, and data fusion. We then develop a theory of estimation and inference for these causal estimands, working under a semiparametric model for the observed data distribution. This is in contrast to the existing work on falsification testing, which is developed in the context of linear regression models and two stage least squares estimation. Our theory yields several novel classes of estimators, which are distinct from those proposed elsewhere in the instrumental variable literature. Our estimators turn out to have a *quadruple robustness* property. Specifically, if the semiparametric model for the causal contrast is correct, then our estimators are unbiased if one out of four sets of additional constraints on the observed data distribution hold. The methods are illustrated in simulation studies and an analysis of the Life Span Study. Our results are closely related to and develop from the *bespoke instrumental variable* design recently proposed in occupational epidemiology (Richardson and Tchetgen Tchetgen, 2021). That work was not developed with specific reference to leveraging negative controls in instrumental variable designs, and lacked general semiparametric estimation and efficiency theory, which we hereby provide. We also give new identification results. This theory may be of independent interest for those working on semiparametric instrumental variable models, as we leverage ideas from unrelated work on generalised odds ratio modelling to construct quadruply robust estimators which to our knowledge has not been done before.

2 Identification

2.1 Bias detection using reference populations

We will first consider a setting where we have i.i.d. copies of a point-treatment exposure A (for the moment assumed to be binary), an end of study outcome Y, a vector of covariates C, and a potentially invalid (and, for the moment, binary) instrument Z. All are measured in a population of interest (S = 1). Suppose furthermore that data are also available on an additional population (S = 0) satisfying a key property given in Assumption 1 below and for which Y and Z are observed. Let Y^a define the potential outcome that would have been observed, had an individual been assigned to intervention level A = a.

In what follows, the population for whom S = 0 will be used to correct for bias that may occur when Z is an invalid instrumental variable. In order to do this, we will first list the assumptions required to detect potential bias, and eventually to identify the causal effect.

Assumption 1. Reference population: Let C_0 (C_1) denote the support of **C** in those with

S = 0 (S = 1). Then $\forall z \in \{0, 1\}$ and $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

$$E(Y|Z = z, S = 0, \mathbf{C} = \mathbf{c}) = E(Y^0|Z = z, S = 0, \mathbf{C} = \mathbf{c}).$$

Assumption 1 states that in the reference population, the conditional expectation of the observed outcome (conditional on Z and \mathbf{C}) is equal to the conditional expectation of the potential outcome under no treatment. This can be plausible if by an exogenous intervention which may be a physical or temporal restriction, individuals were unable to receive treatment. In pharmacoepidemiologic studies, a reference population may be sourced from time periods when a new treatment was not yet available, or from patients not eligible to receive the treatment. Alternatively, in environmental health studies, a natural reference population may be determined based on physical/spatial considerations that would have prevented access to the exposure.

A negative control population where the exposure is not necessarily degenerate but is hypothesised to have no effect, could also form a reference population. However, the concept of a reference population allows for the possibility that the treatment causally impacts the outcome in those with S = 0, if these individuals were not excluded from access to treatment. In general, it is advantageous to choose a reference population that is similar in important baseline characteristics to the S = 1 population. This is because to eventually identify a causal effect, we will need to transport associations across from the reference to the S = 1 population. We emphasise that it is not obvious how other negative control-type designs can generally leverage sub-populations for whom treatment is degenerate. These designs usually involve contrasts between levels of A that are expected to be zero when there is no bias. Hence some variation in exposure is typically required (Lipsitch et al., 2010).

A potential data-generating process is illustrated in the causal diagram in Figure 1.



(a) Target population (S = 1) (b) Reference population (S = 0)

Figure 1: Possible DAG with a reference population

Here, the edges from Z to Y and U to Z in both populations indicate violations of IV.2 and IV.3. As noted in Davies et al. (2017), under Assumption 1 and conditions IV.2 and IV.3 holding in both populations, one would expect a null association between Z and Y in the reference population. This can be formalised as follows:

Proposition 2.0.1. Suppose that $\forall z \in \{0,1\}$ and $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

- If Z = z and S = 1, then $Y^{0,z} = Y$ (instrument consistency).
- $E(Y^{0,z}|Z=z, S=0, \mathbf{C}=\mathbf{c}) = E(Y^{0,z}|S=0, \mathbf{C}=\mathbf{c})$ (unconfoundedness).

• $E(Y^{0,z}|S=0, \mathbf{C}=\mathbf{c}) = E(Y^0|S=0, \mathbf{C}=\mathbf{c})$ (exclusion restriction).

Then under Assumption 1, $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$

$$E(Y|Z = 1, S = 0, \mathbf{C} = \mathbf{c}) = E(Y|Z = 0, S = 0, \mathbf{C} = \mathbf{c}).$$
(1)

See B.1 of the Appendix for a proof. This statement provides the basis of a valid test of IV.2 and IV.3 in the reference population. To draw conclusions about the target

population, we would furthermore need to assume that $\forall z \in \{0, 1\}$ and $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

$$E(Y^{0,z}|Z = z, S = 1, \mathbf{C} = \mathbf{c}) = E(Y^0|S = 1, \mathbf{C} = \mathbf{c})$$

$$\Rightarrow E(Y^{0,z}|Z = z, S = 0, \mathbf{C} = \mathbf{c}) = E(Y^0|S = 0, \mathbf{C} = \mathbf{c}).$$
(2)

In other words, Z is an instrument in S = 0 if it is an instrument in S = 1. Then (1) can be used as the basis of a valid falsification test for the IV assumptions in the target population. If we strengthen (2) to an 'iff' statement and Proposition 2.0.1 to an 'iff' result (under a faithfulness-type condition), then we can construct a consistent test. We note that the proposition allows for the distribution of **C** to differ between populations, but if the support of **C** differs between the standard and reference populations, one may not be able to draw conclusions for all individuals with S = 1.

2.2 Point identification

We will focus on identification of the conditional average treatment effect on the treated in the target population:

$$E(Y^1 - Y^0 | A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}).$$

We focus on conditional effects given that investigators may often be interested in subgroupspecific contrasts. If one is interested in the marginal treatment effect in the treated, our identification and estimation results are still useful since conditional effects can be standardized according to the covariate distributions in the treated arm:

$$E(Y^{1} - Y^{0}|A = 1, S = 1) = E\{E(Y^{1} - Y^{0}|A = 1, Z, S = 1, \mathbf{C})|A = 1, S = 1\}.$$

Further assumptions are required to identify a causal effect.

Assumption 2. Consistency: if A = a and S = 1, then $Y^a = Y$.

Assumption 3. *IV relevance:* $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

$$E(A|Z = 1, S = 1, \mathbf{C} = \mathbf{c}) - E(A|Z = 0, S = 1, \mathbf{C} = \mathbf{c}) \neq 0.$$

Assumption 4. Partial population exchangeability: $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

$$E(Y^{0}|Z = 1, S = 1, \mathbf{C} = \mathbf{c}) - E(Y^{0}|Z = 0, S = 1, \mathbf{C} = \mathbf{c})$$
$$= E(Y^{0}|Z = 1, S = 0, \mathbf{C} = \mathbf{c}) - E(Y^{0}|Z = 0, S = 0, \mathbf{C} = \mathbf{c}).$$

We note first that Assumption 2 is standard in causal inference. Assumption 3 demands that Z is predictive of the exposure; although this assumption is similar to IV.1, Z is not required to satisfy either IV.2 or IV.3. In particular, our assumptions also allow for Z to be a standard confounder with a direct effect on the outcome (violating the exclusion restriction). When IV.2 and IV.3 hold *in both populations*, we note that Assumption 4 then automatically also holds. This is because one can show that under the IV conditions, $E(Y^0|Z = 1, S = s, \mathbf{C} = \mathbf{c}) - E(Y^0|Z = 0, S = s, \mathbf{C} = \mathbf{c}) = 0 \quad \forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1 \text{ and } s = 0, 1.$ Assumption 4 requires that the (conditional) additive association between the potential outcome Y_0 and Z transports between the negative control and target populations. It is not generally testable. We discuss the plausibility of this assumption below, which is weaker than the full population exchangeability assumption made in the transportability literature (Dahabreh et al., 2019).

Remark. To provide some intuition for Assumption 4, in A.1 of the Appendix we consider an example data-generating mechanism based on linear structural models. It indicates how although we are agnostic about whether core conditions IV.2 or IV.3 are violated, knowledge that IV.3 (unconfoundedness) holds could make Assumption 4 more plausible. In that case, the association between Z and Y in the reference population could be interpreted as a direct causal effect; one may be on firmer grounds to transport a causal effect across populations.

Remark. Note that Assumption 4 is related to a more standard 'additive equi-confounding'type assumption:

$$E(Y^{0}|A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) - E(Y^{0}|A = 1, Z = z, S = 0, \mathbf{C} = \mathbf{c})$$
$$= E(Y^{0}|A = 0, Z = z, S = 1, \mathbf{C} = \mathbf{c}) - E(Y^{0}|A = 0, Z = z, S = 0, \mathbf{C} = \mathbf{c})$$
(3)

 $\forall z \in \{0,1\}$ and $\forall \mathbf{c} \in C_0 \cap C_1$ (Sofer et al., 2016), which contrasts Y^0 within levels of A. To interpret (3) in the standard difference-in-differences setting, S plays the role of time and Z is an arbitrary covariate. Assumption 4 does not appear to be stronger nor weaker in general than (3). Both can be motivated by assuming that the (conditional mean) association between an unmeasured confounder U and Y is constant across populations. We defer to A.1 for a more precise discussion, but note that Assumption 4 places restrictions on the (conditional mean) association between Z and Y₀, with different restrictions on the conditional mean of U. It is not obvious how to leverage (3) when there is no variation in A in the reference population (as in our data example). Furthermore, if many candidate Zs are collected, one can then choose between them to obtain identification. In contrast, (3) is restricted to holding for the treatment variable.

Remark. Our assumptions are stated conditional on covariates C. To ensure Assumption 4 holds, we require that C includes all effect modifiers of the additive association between Z and Y^0 that differ in distribution between populations. In terms of design implications, this suggests choosing a reference population that is similar to the target population in terms of characteristics that may modify the association between Z and Y^0 . As argued above, it is also advantageous to incorporate measured confounders for the effect of Z on

Y, as well as for the effect of A on Y, since this may weaken the restrictions on U.

Assumptions 1-4 will be sufficient to test the causal null hypothesis that $E(Y^1 - Y^0|A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) = 0$, as formalised in A.2 of the Appendix. However, they are insufficient to identify the causal effect of interest. Therefore we will posit two additional assumptions; only one is required to hold to yield identification:

Assumption 5. No effect modification (NEM): $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$

$$E(Y^1 - Y^0 | A = 1, Z = 1, S = 1, \mathbf{C} = \mathbf{c}) = E(Y^1 - Y^0 | A = 1, Z = 0, S = 1, \mathbf{C} = \mathbf{c}).$$

Assumption 6. No selection modification (NSM): If we define the selection bias as

$$\gamma(z, \mathbf{c}) \equiv E(Y^0 | A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) - E(Y^0 | A = 0, Z = z, S = 1, \mathbf{C} = \mathbf{c})$$

then $\gamma(1, \mathbf{c}) = \gamma(0, \mathbf{c}) \ \forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1.$

The first of these requires that the conditional average treatment effect on the treated does not depend on Z (Hernán and Robins, 2006), whereas the second assumption requires that the selection bias is not a function of Z (Tchetgen Tchetgen and Vansteelandt, 2013). Then we are in a position to give the main theorem for identification.

Theorem 2.1. Under Assumptions 1 and 4, $t(z, \mathbf{c}) \equiv E(Y^0|Z = z, S = 1, \mathbf{C} = \mathbf{c}) - E(Y^0|Z = 0, S = 1, \mathbf{C} = \mathbf{c})$ is identified as

$$t(z, \mathbf{c}) = E(Y|Z = z, S = 0, \mathbf{C} = \mathbf{c}) - E(Y|Z = 0, S = 0, \mathbf{C} = \mathbf{c})$$

 $\forall z \in \{0,1\}$ and $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$. Further assuming Assumptions 2 and 3, if Assumption 5

holds, then

$$E(Y^{1} - Y^{0}|A = 1, S = 1, \mathbf{C} = \mathbf{c})$$

=
$$\frac{E(Y|Z = 1, S = 1, \mathbf{C} = \mathbf{c}) - E(Y|Z = 0, S = 1, \mathbf{C} = \mathbf{c}) - t(1, \mathbf{c})}{E(A|Z = 1, S = 1, \mathbf{C} = \mathbf{c}) - E(A|Z = 0, S = 1, \mathbf{C} = \mathbf{c})}.$$

Alternatively, if Assumption 6 also holds, then

$$\begin{split} E(Y^{1} - Y^{0}|A &= 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) \\ &= E(Y|A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) - E(Y|A = 0, Z = z, S = 1, \mathbf{C} = \mathbf{c}) \\ &+ \frac{E(Y|A = 0, Z = 1, S = 1, \mathbf{C} = \mathbf{c}) - E(Y|A = 0, Z = 0, S = 1, \mathbf{C} = \mathbf{c}) - t(1, \mathbf{c})}{E(A|Z = 1, S = 1, \mathbf{C} = \mathbf{c}) - E(A|Z = 0, S = 1, \mathbf{C} = \mathbf{c})}. \end{split}$$

A proof is given in B.2 of the Appendix. Note that the identification functional under NEM amounts to the conditional Wald estimand (Wang and Tchetgen Tchetgen, 2018), after transforming the outcome by subtracting $t(z, \mathbf{C})$. Essentially, the bias (learnt in the reference population) is subtracted from the numerator of the Wald estimand, in a similar fashion to what is done in difference-in-differences.

2.3 Negative control outcomes

One can also harness measurements of a negative control outcome in order to generate a reference population. Suppose that there is now only data on individuals from the target population, such that S = 1 for everyone (we omit this from the conditioning statement to simplify notation). Further, suppose that one collects a random variable W in the target population that satisfies the following assumption

$$E(W|Z = z, \mathbf{C} = \mathbf{c}) = E(W^0|Z = z, \mathbf{C} = \mathbf{c})$$
(4)

 $\forall z \in \{0, 1\}$ and $\forall \mathbf{c}$ in the support of \mathbf{C} (Danieli et al., 2022). Intuitively, the observed outcome for W is the same outcome as would be observed under no exposure; this is plausible when scientific expertise suggests there cannot be any exposure effect of Aon W. For example, W could be an outcome occurring before the individual could be exposed. Note that (4) restricts the effect of A on the negative control outcome; so far, nothing is assumed about Z being a valid instrument w.r.t W.

If we additionally assume condition that

$$E(Y^{0}|Z = 1, \mathbf{C} = \mathbf{c}) - E(Y^{0}|Z = 0, \mathbf{C} = \mathbf{c})$$

= $E(W^{0}|Z = 1, \mathbf{C} = \mathbf{c}) - E(W^{0}|Z = 0, \mathbf{C} = \mathbf{c})$ (5)

then it follows from Theorem 2.1 that one can identify the effect $E(Y^1 - Y^0 | A = 1, Z = z, \mathbf{C} = \mathbf{c})$ by leveraging the (conditional) association between the negative control outcome W and Z. Specifically, if we assume that the causal effect does not depend on Z,

$$E(Y^{1} - Y^{0}|A = 1, Z = z, \mathbf{C} = \mathbf{c}) = \frac{E(Y - W|Z = 1, \mathbf{c}) - E(Y - W|Z = 0, \mathbf{c})}{E(A|Z = 1, \mathbf{c}) - E(A|Z = 0, \mathbf{c})}.$$
 (6)

In A.3 of the Appendix, we provide a parallel result when restricting the dependence of the selection bias on Z.

In the case that W is a pre-exposure outcome, Ye et al. (2020) arrive at an expression similar to (6), although they consider a setting where two measurements of the exposure (in addition to the outcome) are available. In the denominator of their expression, the contrast involves the difference in the exposure measurements. In addition, Ye et al. (2020) target a different causal estimand and their identification results are separate from ours; see also Richardson et al. (2023). Their identification functional also appears in the econometrics literature on 'fuzzy' difference-in-differences designs (De Chaisemartin and d'Haultfoeuille, 2018), where it is usually interpreted under separate assumptions as a local average treatment effect.

3 Estimation and inference

3.1 Semiparametric Theory

In this section, we will first develop a novel semiparametric efficiency theory for the conditional treatment effect $E(Y^{\mathbf{a}} - Y^{\mathbf{0}}|\mathbf{A} = \mathbf{a}, \mathbf{Z} = \mathbf{z}, S = 1, \mathbf{C} = \mathbf{c}) = \beta(\mathbf{a}, \mathbf{z}, \mathbf{c})$. We allow for \mathbf{A} , \mathbf{Z} and \mathbf{C} to be continuous or discrete and potentially vector-valued. Our results are distinct from those developed previously in the instrumental variable literature (Robins, 1994; Tchetgen Tchetgen and Vansteelandt, 2013). We note that our model parametrizes treatment effects in different populations; $\beta(\mathbf{a}, \mathbf{z}, \mathbf{c})$ may not equal $\beta(\mathbf{a}', \mathbf{z}, \mathbf{c})$ if $\mathbf{a} \neq \mathbf{a}'$. See Robins (1994) for details on the parametrisation of structural mean models.

We postulate a semiparametric model

$$\beta(\mathbf{a}, \mathbf{z}, \mathbf{c}) = \beta(\mathbf{a}, \mathbf{z}, \mathbf{c}; \psi), \tag{7}$$

where ψ is an unknown finite-dimensional parameter vector with true value ψ^{\dagger} . Then the previous NEM assumption can be generalised as:

Assumption 7. No effect modification (NEM): with probability 1,

$$\beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}) = \beta(\mathbf{A}, \mathbf{C}).$$

We will let \mathcal{M}_{NEM} denote the model defined by restriction (7) along with Assumptions 7 and 8-11, (see A.4 of the Appendix), which are generalised versions of Assumptions 1-4. To simplify the exposition, we work under a NEM assumption in the main manuscript, but parallel results under an NSM assumption are developed in A.5 of the Appendix.

Introducing some notation, let us redefine $t(\mathbf{z}, \mathbf{C}) \equiv E(Y^{\mathbf{0}} | \mathbf{Z} = \mathbf{z}, S = 1, \mathbf{C}) - E(Y^{\mathbf{0}} | \mathbf{Z} = \mathbf{0}, S = 1, \mathbf{C})$. Then, we define the residual

$$\epsilon^* \equiv Y - \beta(\mathbf{A}, \mathbf{C})S - t(\mathbf{Z}, \mathbf{C}) - b_1(\mathbf{C})S - b_0(\mathbf{C})$$

where $t(\mathbf{Z}, \mathbf{C})$ is identified as

$$t(\mathbf{z}, \mathbf{C}) = E(Y|\mathbf{Z} = \mathbf{z}, S = 0, \mathbf{C}) - E(Y|\mathbf{Z} = \mathbf{0}, S = 0, \mathbf{C})$$

under 9-10. Also,

$$b_1(\mathbf{C}) \equiv E\{Y - \beta(\mathbf{A}, \mathbf{C})S | \mathbf{Z} = \mathbf{0}, S = 1, \mathbf{C}\} - E(Y - \beta(\mathbf{A}, \mathbf{C})S | \mathbf{Z} = \mathbf{0}, S = 0, \mathbf{C})$$

 $b_0(\mathbf{C}) \equiv E(Y | \mathbf{Z} = \mathbf{0}, S = 0, \mathbf{C}).$

. We use the notation $\epsilon^*(\psi^{\dagger})$ when $\beta(\mathbf{A}, \mathbf{C}; \psi^{\dagger})$ replaces $\beta(\mathbf{A}, \mathbf{C})$ in ϵ^* .

Theorem 3.1. Under the semiparametric model \mathcal{M}_{NEM} , the orthocomplement to the nuisance tangent space is given as

$$\left\{\phi(\mathbf{Z}, S, \mathbf{C})\epsilon^*(\psi^{\dagger}) : \phi(\mathbf{Z}, S, \mathbf{C}) \in \Omega\right\} \cap L_2^0$$

where

$$\Omega = \{\phi(\mathbf{Z}, S, \mathbf{C}) : E\{\phi(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\} = E\{\phi(\mathbf{Z}, S, \mathbf{C}) | S, \mathbf{C}\} = 0\}$$

and L_2^0 is the Hilbert space of zero mean, finite variance functions with dimension $\dim(\psi^{\dagger})$.

A proof is given in B.3 of the Appendix. As reviewed e.g. in Bickel et al. (1993), by deriving the orthocomplement of the nuisance tangent space, we obtain the class of influence functions of all regular and asymptotically linear (RAL) estimators of ψ^{\dagger} . In turn, knowing this class motivates the construction of RAL estimators e.g. by solving estimating equations based on a chosen influence function. Specifically, under Assumption 7, we can estimate ψ^{\dagger} as the solution to the equations

$$0 = \sum_{i=1}^{n} \phi(\mathbf{Z}_i, S_i, \mathbf{C}_i) \epsilon_i^*(\psi^{\dagger})$$

for a chosen $\phi(\mathbf{Z}, S, \mathbf{C})$ that satisfies the above restrictions.

Converting the above result into an estimation strategy requires a choice of $\phi(\mathbf{Z}, S, \mathbf{C})$. In order to give a closed-form representation of Ω , we first provide a definition.

Definition 1. Admissible Independence Density (Tchetgen Tchetgen et al., 2010). Consider three potentially vector-valued random variables \mathbf{X}_1 , \mathbf{X}_2 and \mathbf{X}_3 . Let $f^{\ddagger}(\mathbf{X}_1, \mathbf{X}_2 | \mathbf{X}_3) = f^{\ddagger}(\mathbf{X}_1 | \mathbf{X}_3) f^{\ddagger}(\mathbf{X}_2 | \mathbf{X}_3)$ denote a fixed density that makes \mathbf{X}_1 and \mathbf{X}_2 conditionally independent given \mathbf{X}_3 . Then $f^{\ddagger}(\mathbf{X}_1, \mathbf{X}_2 | \mathbf{X}_3)$ is an admissible independence density if it is absolutely continuous with respect to the true joint law $f(\mathbf{X}_1, \mathbf{X}_2 | \mathbf{X}_3)$ with probability 1.

It follows from Tchetgen Tchetgen et al. (2010) that, for the admissible independence density $f^{\ddagger}(\mathbf{Z}, S | \mathbf{C})$ we have

$$\Omega = \left\{ \frac{f^{\ddagger}(\mathbf{Z}, S | \mathbf{C})}{f(\mathbf{Z}, S | \mathbf{C})} [r_0(\mathbf{Z}, S, \mathbf{C}) - E^{\ddagger} \{r_0(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C} \} - E^{\ddagger} \{r_0(\mathbf{Z}, S, \mathbf{C}) | S, \mathbf{C} \} + E^{\ddagger} \{r_0(\mathbf{Z}, S, \mathbf{C}) | \mathbf{C} \}] : r_0(\mathbf{Z}, S, \mathbf{C}) \text{ unrestricted} \right\}$$
(8)

where $E^{\ddagger}(\cdot|\cdot)$ denotes a (conditional) expectation taken with respect to $f^{\ddagger}(\cdot|\cdot)$. To construct an estimator, one can choose any $f^{\ddagger}(\mathbf{Z}, S|\mathbf{C})$ that satisfies the above definition. The optimal choice of $r_0(\mathbf{Z}, S, \mathbf{C})$ for efficiency can nevertheless depend on the choice of $f^{\ddagger}(\mathbf{Z}, S|\mathbf{C})$. But there is no requirement to select the true densities, as the following example shows. **Example 1.** Let \mathbf{Z} be binary, and suppose one sets $f^{\ddagger}(Z = 1|\mathbf{C}) = f^{\ddagger}(S = 1|\mathbf{C}) = 0.5$ and chooses $r_0(Z, S, \mathbf{C}) = 16(Z - 0.5)(S - 0.5)m(\mathbf{C})$. Then one can estimate ψ via the unbiased estimating function

$$\frac{m(\mathbf{C})(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\epsilon^*(\psi^{\dagger}) \tag{9}$$

Equation (9) suggests a simple and practical choice of estimating function for binary Z, which we use in our simulations and data analysis.

3.2 De-biased machine learning and multiply robust estimation

The estimation strategies previously described are not generally feasible, because the estimating equations for ψ^{\dagger} involve nuisance parameters that are typically unknown. One approach to deal with this is to plug-in estimates obtained from nonparametric estimators or flexible statistical learning methods (Chernozhukov et al., 2018). In A.6 of the Appendix, we therefore use Theorem 3.1 to construct cross-fit de-biased machine learning-based estimators of ψ^{\dagger} , and describe sandwich estimators of the asymptotic variance. Nevertheless, to develop a more nuanced understanding of the different bias properties of RAL estimators of ψ^{\dagger} , we will instead consider a scenario where parametric working models are used for the conditional expectations/densities that arise in estimating the causal effect of interest. We hence conceptualise bias as potentially arising from parametric model misspecification. The parametric approach will also suggest how nuisance functions should be estimated nonparametrically for optimal performance in terms of their convergence rates.

Let us define the following parametric models $t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})$ for $t(\mathbf{Z}, \mathbf{C})$, $b_0(\mathbf{C}; \theta_0^{\dagger})$ for $b_0(\mathbf{C})$ and $b_1(\mathbf{C}; \theta_1^{\dagger})$ for $b_1(\mathbf{C})$ that are required to model the conditional outcome mean for both the S = 1 and S = 0 populations. Here, $t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})$, $b_0(\mathbf{C}; \theta_0^{\dagger})$ and $b_1(\mathbf{C}; \theta_1^{\dagger})$

are known functions, which are smooth in ν^{\dagger} , θ_0^{\dagger} and θ_1^{\dagger} respectively. We will sometimes use the notation $\theta^{\dagger} = (\theta_1^{\dagger^T}, \theta_0^{\dagger^T})^T$. For modelling the joint conditional density $f(\mathbf{Z}, S | \mathbf{C})$, we will make use of the following parametrisation based on the generalised odds ratio function

$$OR(\mathbf{Z}, S, \mathbf{C}) = \frac{f(\mathbf{Z}|S, \mathbf{C})f(\mathbf{Z} = \mathbf{z_0}|S = s_0, \mathbf{C})}{f(\mathbf{Z} = \mathbf{z_0}|S, \mathbf{C})f(\mathbf{Z}|S = s_0, \mathbf{C})}$$

(Tchetgen Tchetgen et al., 2010). The reference values of \mathbf{z}_0 and s_0 are user-specified; in what fallows, we will use $\mathbf{z}_0 = \mathbf{0}$ and $s_0 = 0$ as a generic notation. Then by specifying $OR(\mathbf{Z}, S, \mathbf{C}), f(\mathbf{Z}|S = 0, \mathbf{C})$ and $f(S|\mathbf{Z} = \mathbf{0}, \mathbf{C})$, one can generate $f(\mathbf{Z}, S|\mathbf{C})$ as

$$f(\mathbf{Z}, S|\mathbf{C}) = \frac{OR(\mathbf{Z}, S, \mathbf{C})f(\mathbf{Z}|S=0, \mathbf{C})f(S|\mathbf{Z}=0, \mathbf{C})}{\int OR(\mathbf{z}, s, \mathbf{C})f(\mathbf{z}|S=0, \mathbf{C})f(s|\mathbf{Z}=0, \mathbf{C})d\mathbf{z}ds}$$

(Chen, 2007) as well as $f(\mathbf{Z}|S, \mathbf{C})$ and $f(S|\mathbf{Z}, \mathbf{C})$. This parametrisation of the joint density will be crucial in constructing estimators with superior robustness properties. We postulate smooth parametric models $f(\mathbf{Z}|S = 0, \mathbf{C}; \tau^{\dagger})$, $f(S|\mathbf{Z} = \mathbf{0}, \mathbf{C}; \alpha^{\dagger})$ and $OR(\mathbf{Z}, S, \mathbf{C}; \rho)$ for $f(\mathbf{Z}|S = 0, \mathbf{C})$, $f(S|\mathbf{Z} = \mathbf{0}, \mathbf{C})$ and $OR(\mathbf{Z}, S, \mathbf{C})$ respectively. We note that ν^{\dagger} , θ^{\dagger} , τ^{\dagger} , α^{\dagger} and ρ^{\dagger} are all finite dimensional parameters.

Consider the following sets of restrictions on the observed data distribution:

- \mathcal{M}_1 : $t(\mathbf{Z}, \mathbf{C}) = t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}), b_0(\mathbf{C}) = b_0(\mathbf{C}; \theta_0^{\dagger}) \text{ and } b_1(\mathbf{C}) = b_1(\mathbf{C}; \theta_1^{\dagger}).$
- \mathcal{M}_2 : $f(\mathbf{Z}|S=0, \mathbf{C}) = f(\mathbf{Z}|S=0, \mathbf{C}; \tau^{\dagger}), OR(\mathbf{Z}, S, \mathbf{C}) = OR(\mathbf{Z}, S, \mathbf{C}; \rho^{\dagger})$ and $t(\mathbf{Z}, \mathbf{C}) = t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}).$
- \mathcal{M}_3 : $f(S|\mathbf{Z} = 0, \mathbf{C}) = f(S|\mathbf{Z} = 0, \mathbf{C}; \alpha^{\dagger}), \ OR(\mathbf{Z}, S, \mathbf{C}) = OR(\mathbf{Z}, S, \mathbf{C}; \rho^{\dagger}), \ \text{and} \ b_1(\mathbf{C}) = b_1(\mathbf{C}; \theta_1^{\dagger}).$
- \mathcal{M}_4 : $f(\mathbf{Z}|S=0, \mathbf{C}) = f(\mathbf{Z}|S=0, \mathbf{C}; \tau^{\dagger}), f(S|\mathbf{Z}=0, \mathbf{C}) = f(S|\mathbf{Z}=0, \mathbf{C}; \alpha^{\dagger})$ and $OR(\mathbf{Z}, S, \mathbf{C}) = OR(\mathbf{Z}, S, \mathbf{C}; \rho^{\dagger}).$

At one extreme, \mathcal{M}_1 requires a correct conditional mean model for outcome after removing the treatment effect: $E\{Y-\beta(\mathbf{A}, \mathbf{C})S|\mathbf{Z}, S, \mathbf{C}\}$. At the other, \mathcal{M}_4 requires a correct model for the joint conditional density $f(\mathbf{Z}, S|\mathbf{C})$. However, we allow for certain combinations of restrictions on these laws. If our model $f(S|\mathbf{Z}, \mathbf{C})$ is correct, then under \mathcal{M}_3 , assumptions on the impact of \mathbf{Z} on the conditional mean of Y given \mathbf{C} in the reference population can be relaxed.

Our goal is to construct an estimator that is quadruply robust, that is, unbiased if one of these four restrictions on the observed data (in addition to model \mathcal{M}_{NEM}) holds. To achieve this, in A.7 in the Appendix we describe an estimation strategy for ψ^{\dagger} , which relies on estimators of ρ^{\dagger} , ν^{\dagger} and θ_1^{\dagger} that are themselves doubly robust. This means that we can obtain an unbiased estimator of $t(\mathbf{Z}, \mathbf{C})$ even when $b_1(\mathbf{C})$ is misspecified (and vice versa). Likewise, we can obtain an unbiased estimate of $f(\mathbf{Z}|S,C)$ even when $f(S|\mathbf{Z} = \mathbf{0}, C)$ is poorly modelled. Indeed, quadruple (rather than triple) robustness hinges on the specific parametrisation of the joint density $f(\mathbf{Z}, S|\mathbf{C})$ using odds ratios.

Theorem 3.2. Under the union model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_2 \cup \mathcal{M}_3 \cup \mathcal{M}_4)$ and assuming standard regularity conditions hold, $\hat{\psi}_{MR-NEM}$ is a consistent and asymptotically normal (CAN) estimator of ψ^{\dagger} .

A proof is given in B.4 of the Appendix. A nonparametric estimator of the standard error for $\hat{\psi}_{MR-NEM}$ can be obtained either using a sandwich estimator, following standard M-estimation theory. Alternatively, one can use the nonparametric bootstrap. Suitable regularity conditions can be found e.g. in Appendix B of Robins et al. (1994). In A.8 of the Appendix, we obtain the semiparametric efficiency bound and the optimal choice of $m(\mathbf{C})$.

Our estimation theory has focused the reference population setting, to avoid repetition and because our estimators simplify in the case of negative control outcomes; see A.9 of the Appendix. In this case, the resulting estimators simplify further and are closely related to the g-estimators of Robins (1994). They are doubly rather than quadruply robust, as fewer nuisance parameters are required to be estimated. Specifically, under NEM either the conditional mean models involving \mathbf{Z} or Y - W need to be correctly specified, in addition to the semiparametric structural model. In A.10 we develop a semiparametric estimation theory for the marginal average treatment effect in the treated.

4 Data analysis

The Life Span Study of atomic bomb survivors in Japan has been influential among in understanding the impact of exposure to high levels of radiation on long-term health outcomes. However, initial analyses overlooked the potential role of confounding; it has been hypothesised that certain socioeconomic factors were associated both with location at the time of the bombing and the longer-term risk of cancer (Richardson, 2012). The dataset contains limited information on potential confounders. On the other hand, there was data collected on residents who were not present in these cities at the time of the bombings, which forms a natural reference population.

We used a sample of 8,463 survivors who were 45-49 years old at the time of the bombings and who were followed up to December 31, 2000. These individuals were residents of Hiroshima or Nagasaki; out of the this sample, 1,787 people were away from the cities at the time of the bombing. A measure of high vs. low exposure to prompt radiation was based on weighted DS02 colon dose estimates, expressed as the weighted dose in gray (Gy); those in the reference population were assumed to have dose estimates equal to 0 Gy. For those who were present in the cities, an individual was considered to have had a high level of exposure if their dose estimates were above the median. The outcome of interest was age at death, measured in years.

We chose city of residence as a potential instrument, since it was strongly predictive

of the exposure and it seemed plausible that the its association with age at death under low radiation exposure could be stable across the two populations. However, we may not expect it to satisfy the exclusion restriction nor unconfoundedness. We adjusted for sex as a covariate. We compared six estimators, described further in C.1 of the Appendix:

- $\hat{\psi}_{TSLS}$: a two-stage least squares estimator that is unbiased under $\mathcal{M}_{NEM} \cap \mathcal{M}_1$.
- $\hat{\psi}_{g-Z}$: a g-estimator that is unbiased under $\mathcal{M}_{NEM} \cap \mathcal{M}_2$.
- $\hat{\psi}_{g-S}$: a g-estimator that is unbiased under $\mathcal{M}_{NEM} \cap \mathcal{M}_3$.
- $\hat{\psi}_{IPW}$: an inverse probability weighted estimator that is unbiased under $\mathcal{M}_{NEM} \cap \mathcal{M}_4$.
- $\hat{\psi}_{MR}$: the multiply-robust estimator described in Section 3.2 with m(C) = 1
- $\hat{\psi}_{MR-eff}$: the multiply-robust estimator with m(C) set to the efficient choice.

Since both variables were binary in this case, it was possible to carry out a fully nonparametric analysis. Nevertheless, a treatment effect under NEM was chosen which excluded an interaction between A and C. Further, to evaluate sensitivity to model misspecification, we considered five different model specifications for the nuisance parameters:

- 1. All working models for the nuisance parameters were saturated.
- 2. The models $OR(Z, S, C; \rho^{\dagger})$ and $t(Z, C; \nu^{\dagger})$ excluded interactions between Z and C.
- 3. The models $OR(Z, S, C; \rho^{\dagger})$, $b_1(C; \theta_1^{\dagger})$ excluded interactions between Z and C.
- 4. The models $t(Z, C; \nu^{\dagger})$, $b_1(C; \theta_1^{\dagger})$ excluded an interaction between Z and C.
- 5. All working models for the nuisance parameters excluded interactions between Z and C.

Varying the fitted models in this way enabled us to check the robustness of the estimators $\hat{\psi}_{TSLS}$, $\hat{\psi}_{g-Z}$, $\hat{\psi}_{g-S}$, $\hat{\psi}_{IPW}$, $\hat{\psi}_{MR}$ and $\hat{\psi}_{MR-eff}$ to departures from a nonparametric model. We note that if all true underlying models for the nuisance parameters include interactions, then in theory one can only construct estimators that are unbiased under the first and fourth specifications. To check sensitivity, we calculated the change in each estimator from estimates based on the first specification (saturated models), then scaling by the latter estimates.

The results of the analysis can be found in Table 1. As might be expected, when all working models are saturated (except the exposure effect model), the estimates are in reasonable agreement. Fitting a linear model adjusted for radiation exposure, city of residence, sex and an interaction between the covariates yielded an exposure effect estimate of -0.32 (95% CI: -0.82, 0.21). A two-stage least squares assumption under the assumption that city was a valid instrument yielded an estimate of 3.48 (95% CI: 2.00, 4.96). Hence the estimates from our analysis tended to be arguably more plausible than from the alternative analyses, albeit with much wider confidence intervals. As one varies the model specifications, one can see the the multiply robust estimators produce stable estimates; in contrast, $\hat{\psi}_{g-Z}$, $\hat{\psi}_{g-S}$, $\hat{\psi}_{IPW}$ all appear to be highly sensitive to departures from fitting saturated models.

5 Discussion

In this article we have proposed strategies for identifying causal effects in studies prone to unmeasured confounding by leveraging both invalid instrumental variables and a reference population. Our notion of a reference population includes negative control populations (for whom the treatment has a null effect) as a special case. In this identification strategy, one must restrict either the conditional average treatment effect on the treated or the se-

Table 1: Results from the Life Span study for the conditional effect in the treated. 95% CI: 95% confidence interval; % Change: absolute percentage change from estimate based on saturated nuisance models.

| Specification | Estimator | Estimate | 95% CI | % Change |
|--|-----------------------|----------|---------------|----------|
| All models saturated | $\hat{\psi}_{TSLS}$ | -1.81 | (-5.32, 1.69) | 0 |
| | $\hat{\psi}_{g-Z}$ | -1.81 | (-5.32, 1.69) | 0 |
| | $\hat{\psi}_{g-S}$ | -1.87 | (-5.38, 1.63) | 0 |
| | $\hat{\psi}_{IPW}$ | -1.82 | (-5.32, 1.67) | 0 |
| | $\hat{\psi}_{MR}$ | -1.82 | (-5.32, 1.67) | 0 |
| | $\hat{\psi}_{MR-eff}$ | -1.87 | (-5.37, 1.64) | 0 |
| $OR(Z, S, C; \rho^{\dagger}), t(Z, C; \nu^{\dagger})$ restricted | $\hat{\psi}_{TSLS}$ | -1.82 | (-5.32, 1.67) | 0.01 |
| | $\hat{\psi}_{g-Z}$ | -2.35 | (-5.89, 1.2) | 0.3 |
| | $\hat{\psi}_{g-S}$ | -2.37 | (-5.92, 1.18) | 0.26 |
| | $\hat{\psi}_{IPW}$ | -4.04 | (-8.44, 0.36) | 1.21 |
| | $\hat{\psi}_{MR}$ | -1.82 | (-5.31, 1.66) | < 0.01 |
| | $\hat{\psi}_{MR-eff}$ | -1.85 | (-5.34, 1.65) | 0.01 |
| $OR(Z, S, C; \rho^{\dagger}), b_1(C; \theta_1^{\dagger})$ restricted | $\hat{\psi}_{TSLS}$ | -1.82 | (-5.33, 1.68) | 0.01 |
| | $\hat{\psi}_{g-Z}$ | -6.29 | (-14.3, 1.71) | 2.47 |
| | $\hat{\psi}_{g-S}$ | -2.37 | (-5.92, 1.18) | 0.27 |
| | $\hat{\psi}_{IPW}$ | -4.04 | (-8.44, 0.36) | 1.21 |
| | $\hat{\psi}_{MR}$ | -1.84 | (-5.34, 1.67) | 0.01 |
| | $\hat{\psi}_{MR-eff}$ | -1.86 | (-5.35, 1.64) | < 0.01 |
| $t(Z,C;\nu^{\dagger}), b_1(C;\theta_1^{\dagger})$ restricted | $\hat{\psi}_{TSLS}$ | -1.83 | (-5.33, 1.66) | 0.01 |
| | $\hat{\psi}_{g-Z}$ | -1.82 | (-5.32, 1.67) | 0.01 |
| | $\hat{\psi}_{g-S}$ | -1.81 | (-5.31, 1.69) | 0.03 |
| | $\hat{\psi}_{IPW}$ | -1.82 | (-5.32, 1.67) | 0 |
| | $\hat{\psi}_{MR}$ | -1.82 | (-5.32, 1.67) | 0 |
| | $\hat{\psi}_{MR-eff}$ | -1.87 | (-5.37, 1.64) | 0 |
| All models restricted | $\hat{\psi}_{TSLS}$ | -1.83 | (-5.33, 1.66) | 0.01 |
| | $\hat{\psi}_{g-Z}$ | -2.35 | (-5.89, 1.2) | 0.3 |
| | $\hat{\psi}_{g-S}$ | -2.37 | (-5.92, 1.18) | 0.27 |
| | $\hat{\psi}_{IPW}$ | -4.04 | (-8.44, 0.36) | 1.21 |
| | $\hat{\psi}_{MR}$ | -1.84 | (-5.33, 1.65) | 0.01 |
| | $\hat{\psi}_{MR-eff}$ | -1.86 | (-5.36, 1.63) | < 0.01 |

lection bias not to depend on \mathbf{Z} . Which restriction one chooses will depend to some extent on *a priori* information on the choice of \mathbf{Z} , but will also be a matter of taste. Restrictions on the treatment effect are perhaps less appealing than in the standard instrumental variable set-up, where the instrument-outcome relationship is already constrained via the exclusion restriction. On the other hand, under NEM, the semiparametric model \mathcal{M}_{NEM} is at least guaranteed to be correctly specified under the null hypothesis. A limitation of the semiparametric theory presented here is that it requires a correctly specified model for the conditional average treatment effect on the treated. We have adopted this framework as it gives us greater flexibility in allowing for arbitrary \mathbf{A} and \mathbf{Z} .

There are also interesting connections with the proximal inference framework (Miao et al., 2018; Tchetgen Tchetgen et al., 2024). Here, a negative control outcome and exposure can together be leveraged to obtain nonparametric identification without a parallel trends assumption. In our case \mathbf{Z} is a potentially invalid negative control exposure. Moreover, when the reference population is a negative control population, the negative control outcome is simply given by (1-S)Y, but because it is not measured in the target population, proximal inference cannot be directly applied. Hence our proposal can be viewed as an alternative to proximal inference where the negative control outcome is missing in the target population and the negative control exposure is invalid.

Finally, one may wish to supplement our proposals with a sensitivity analysis. Attention may be given in particular to the crucial assumption of partial population exchangeability; one could then proceed by parametrising deviations from this condition. With multiple invalid instrumental variables, the average treatment effect on the treated may become over identified, and specification tests (like the Sargen-Hansen test) can then be employed to assess the validity of the identifying assumptions described here. If one has access to multiple reference populations, then one could compare associations between \mathbf{Z} and Y across the different populations. If associations of similar magnitudes are observed, this would provide support for the partial population exchangeability. This same idea motivates pre-trend tests in difference-in-difference designs. How to optimally combine or synthesise evidence from multiple invalid instrumental variables by leveraging negative controls is also an important area for future work.

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Appendix

A Additional information

A.1 Linear structural equation models

Consider the following models for the data-generating process:

$$E(Y^{0}|Z, S = s, \mathbf{C}, U) = \zeta_{0,s} + \zeta_{1,s}Z + \zeta_{2,s}\mathbf{C} + \zeta_{3,s}U$$
$$E(U|Z, S = s, \mathbf{C}) = v_{0,s} + v_{1,s}Z + v_{2,s}\mathbf{C}$$
(10)

for s = 0, 1. If we first consider a conditional parallel trends or 'additive equi-confounding' condition (3), note that (3) can be shown to hold if $\zeta_{3,0} = \zeta_{3,1}$ and

$$E(U|A = 1, Z, S = 1, \mathbf{C}) - E(U|A = 0, Z, S = 1, \mathbf{C})$$
(11)

$$= E(U|A = 1, Z, S = 0, \mathbf{C}) - E(U|A = 0, Z, S = 0, \mathbf{C})$$
(12)

with probability 1. Here, we are also assuming $Y^0 \perp A | Z, S, \mathbf{C}, U$ for z = 0, 1 (latent conditional exchangeability of treatment). Hence (3) can be justified under model (10) if the (conditional mean) association between outcome under control and the unmeasured confounder transports between the target and reference populations. The (conditional mean) association between U and A should also be equal across populations.

Consider now a full population exchangeability condition (Dahabreh et al., 2019): $\forall z \in \{0, 1\}$ and $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

$$E(Y^{0}|Z = z, S = 1, \mathbf{C} = \mathbf{c}) = E(Y^{0}|Z = z, S = 0, \mathbf{C} = \mathbf{c}),$$
(13)

then since

$$E(Y^{0}|Z, S = s, \mathbf{C}) = \zeta_{0,s} + \zeta_{3,s}v_{0,s} + (\zeta_{1,s} + \zeta_{3,s}v_{1,s})Z + (\zeta_{2,s} + \zeta_{3,s}v_{2,s})\mathbf{C}$$

for s = 0, 1, a sufficient condition for (13) to hold is that $\zeta_{i,0} = \zeta_{i,1}$ for i = 0, ..., 3 and $v_{j,0} = v_{j,1}$ for j = 0, 1, 2. Hence in the presence of an unmeasured variable U, we require all associations encoded by the coefficients in (10) to transport across populations. We note that beyond model (10), Assumption 4 is weaker than full population exchangeability since it only restricts the additive interaction between Z and S with respect to the conditional mean of Y^0 .

Moving now to the partial population exchangeability Assumption 4 in the main manuscript, note that in contrast to the above, this requires only that $\zeta_{1,0} = \zeta_{1,1}, \zeta_{3,0} = \zeta_{3,1}$ and $v_{2,0} = v_{2,1}$. Some remarks below:

- Suppose that $Y^{0,z} \perp Z | S, \mathbf{C}, U$ for z = 0, 1 (latent conditional exchangeability of the instrument). Then in (10), $\zeta_{1,0}$ and $\zeta_{1,1}$ represent the direct effects of Z on Y^0 in each population.
- Suppose that the previous condition is strengthened to Y^{0,z}⊥⊥Z|S, C for z = 0, 1 with probability one (conditional exchangeability of the instrument). Then Assumption 4 requires only that ζ_{1,0} = ζ_{1,1}. Hence in this case, the direct causal effect of Z should transport, and no restrictions are placed on the unmeasured confounder.
- Suppose that ∀z, Y^{0,z} = Y⁰ (exclusion restriction). Then ζ_{1,0} = ζ_{1,1} = 0 under the exclusion restriction. Hence Assumption 4 restricts the (conditional mean) association between Y₀ and U, as was done to justify (3), as well as the (conditional mean) association between Z and U.
- In this context, both additive equi-confounding (3) and Assumption 4 require that

 $\zeta_{3,0} = \zeta_{3,1}$. However, (3) is justified under (11) whereas Assumption 4 requires that $v_{1,0} = v_{1,1}$ as well as $\zeta_{1,0} = \zeta_{1,1}$.

A.2 Results for hypothesis testing

Theorem A.1. Under Assumptions 1-4, then if

$$E(Y^{1} - Y^{0}|A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) = 0$$
(14)

 $\forall z \in \{0,1\}, c \in \mathcal{C}_0 \cap \mathcal{C}_1, \text{ then it follows that}$

$$E\{Y - t(Z, \mathbf{c}) | Z = 1, S = 1, \mathbf{c}\} = E\{Y - t(Z, \mathbf{c}) | Z = 0, S = 1, \mathbf{c}\}.$$
(15)

A proof is given in section B.5.

A.3 Negative control outcomes - identification

If we assume

$$E\{Y^{0}|A=1, Z, \mathbf{C}\} - E\{Y^{0}|A=0, Z, \mathbf{C}\} = \gamma(\mathbf{C})$$
(16)

then we have

$$\begin{split} &E\{Y^{1} - Y^{0} | A = 1, Z = z, \mathbf{C} = \mathbf{c}\} \\ &= E\{Y | A = 1, z, \mathbf{c}\} - E\{Y | A = 0, z, \mathbf{c}\} \\ &+ \frac{E\{Y | A = 0, Z = 1, \mathbf{c}\} - E\{Y | A = 0, Z = 0, \mathbf{c}\}}{E(A | Z = 1, \mathbf{c}) - E(A | Z = 0, \mathbf{c})} - \frac{E\{W | Z = 1, \mathbf{c}\} - E\{W | Z = 0, \mathbf{c}\}}{E(A | Z = 1, \mathbf{c}) - E(A | Z = 0, \mathbf{c})}. \end{split}$$

A.4 Assumptions for a general instrumental variable model

Assumption 8. Reference population:

$$E(Y|\mathbf{Z}, S = 0, \mathbf{C}) = E(Y^{0}|\mathbf{Z}, S = 0, \mathbf{C})$$

with probability 1.

Assumption 9. Consistency: $Y = Y^{\mathbf{A}}$ with probability 1 in those with S = 1.

Assumption 10. Relevance: $\mathbf{A} \not\perp \mathbf{Z} | \mathbf{C}, S = 1$ with probability 1.

Assumption 11. Partial population exchangeability:

$$E(Y^{0}|\mathbf{Z} = \mathbf{z}, S = 1, \mathbf{C}) - E(Y^{0}|\mathbf{Z} = \mathbf{0}, S = 1, \mathbf{C})$$
$$= E(Y^{0}|\mathbf{Z} = \mathbf{z}, S = 0, \mathbf{C}) - E(Y^{0}|\mathbf{Z} = \mathbf{0}, S = 0, \mathbf{C})$$

with probability 1.

A.5 Estimation under NSM

We will proceed under a generalised version of the NSM assumption:

Assumption 12. No selection modification (NSM):

The generalised selection bias function

$$q(\mathbf{a}, \mathbf{Z}, \mathbf{C}) = E(Y^{0} | \mathbf{A} = \mathbf{a}, \mathbf{Z}, S = 1, \mathbf{C}) - E(Y^{0} | \mathbf{A} = \mathbf{0}, \mathbf{Z}, S = 1, \mathbf{C})$$

satisfies the restriction $q(\mathbf{a}, \mathbf{Z}, \mathbf{C}) = q(\mathbf{a}, \mathbf{C})$.

Let us define

$$\epsilon \equiv Y - \beta(\mathbf{A}, \mathbf{Z}, \mathbf{C})S - [q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}]S$$
$$- t(\mathbf{Z}, \mathbf{C}) - b_1(\mathbf{C})S - b_0(\mathbf{C})$$

where

$$b_1(\mathbf{C}) \equiv E(Y^0 | \mathbf{Z} = \mathbf{0}, S = 1, \mathbf{C}) - E(Y^0 | \mathbf{Z} = \mathbf{0}, S = 0, \mathbf{C})$$

 $b_0(\mathbf{C}) \equiv E(Y^0 | \mathbf{Z} = \mathbf{0}, S = 0, \mathbf{C}).$

Then the orthocomplement to the nuisance tangent space under NSM can be obtained via the following extension of Theorem 3.1.

Theorem A.2. The orthocomplement to the nuisance tangent space under model \mathcal{M}_{NSM} is given by

$$\left\{ \left\{ S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) + \phi(\mathbf{Z}, S, \mathbf{C}) \right\} \epsilon(\psi^{\dagger}) + S\phi(\mathbf{Z}, S, \mathbf{C}) [q(\mathbf{A}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}] \\ : \kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) \in \Gamma, \phi(\mathbf{Z}, S, \mathbf{C}) \in \Omega \right\} \cap L_2^0$$

where

$$\Gamma = \left\{ \kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) : E\{\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C} \right\} = E\{\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{A}, S = 1, \mathbf{C} \} = 0 \right\}.$$

A proof is given in section B.6.

Under the NSM assumption, we will utilise an additional parametric model $q(\mathbf{A}, \mathbf{C}; \omega^{\dagger})$ for the selection bias function $q(\mathbf{A}, \mathbf{C})$, where $q(\mathbf{A}, \mathbf{C}; \omega^{\dagger})$ is a known function smooth in a finite dimensional parameter ω^{\dagger} . A smooth model $f(\mathbf{A}|\mathbf{Z}, S = 1, \mathbf{C}; \pi^{\dagger})$ is postulated for $f(\mathbf{A}, \mathbf{Z}|S = 1, \mathbf{C})$; the event that model $f(A|\mathbf{Z}, S, \mathbf{C}; \pi^{\dagger})$ is correctly specified is denoted by \mathcal{M}_a . We will also consider alternative versions of the previous restrictions \mathcal{M}_{1q} and \mathcal{M}_{3q} on the data:

- \mathcal{M}_{1q} : $t(\mathbf{Z}, \mathbf{C}) = t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}), \ b_0(\mathbf{C}) = b_0(\mathbf{C}; \theta_0^{\dagger}), \ b_1(\mathbf{C}) = b_1(\mathbf{C}; \theta_1^{\dagger}) \ \text{and} \ q(\mathbf{A}, \mathbf{C}) = q(\mathbf{A}, \mathbf{C}; \omega^{\dagger}).$
- \mathcal{M}_{3q} : $f(S|\mathbf{Z}=0,\mathbf{C}) = f(S|\mathbf{Z}=0,\mathbf{C};\alpha^{\dagger}), OR(\mathbf{Z},S,\mathbf{C}) = OR(\mathbf{Z},S,\mathbf{C};\rho^{\dagger}), b_1(\mathbf{C}) = b_1(\mathbf{C};\theta_1^{\dagger}), \text{ and } q(\mathbf{A},\mathbf{C}) = q(\mathbf{A},\mathbf{C};\omega^{\dagger}).$

In order to estimate nuisance parameters and then obtain $\hat{\psi}_{MR-NSM}$ under NSM, one can use the strategy described in Section A.7.

Theorem A.3. Under the union $\mathcal{M}_{NSM} \cap \mathcal{M}_a \cap (\mathcal{M}_{1q} \cup \mathcal{M}_2 \cup \mathcal{M}_{3q} \cup \mathcal{M}_4)$ and standard regularity conditions, $\hat{\psi}_{MR-NSM}$ is a CAN estimator of ψ^{\dagger} .

A proof is given in section B.7. Hence, we can obtain a similar quadruple robustness result under the NSM assumption, although we now require a correctly specified propensity score model. Note that a similar parametrisation of the joint density $f(\mathbf{A}, \mathbf{Z}|S = 1, \mathbf{C})$ based on the generalised odds ratio function could be used here. Nevertheless, since one needs to model $f(\mathbf{A}|\mathbf{Z}, S = 1, \mathbf{C})$ correctly in order to obtain an unbiased estimator, adopting such a parametrisation will not generally lead to greater robustness. Finally, since estimation under NSM requires consistent estimation of the propensity score, one approach would be to use flexible nonparametric/machine learning methods of $f(\mathbf{A}|\mathbf{Z}, S = 1, \mathbf{C})$ combined with cross-fitting, even if one were to then use parametric models for the other nuisance parameters. Under NSM, there appears to exist no closed-form expression for the efficient score for arbitrary **A** and **Z**.

A.6 Algorithm for constructing cross-fit de-biased machine learning estimators

If all nuisance parameter estimators converge at a rate faster than $n^{-1/4}$ and samplesplitting/cross-fitting is used, then the resulting estimators of ψ^{\dagger} are RAL with variance equal to the variance of its influence function; see e.g. Chernozhukov et al. (2018) for a review.

In what follows, let $\mathbf{O} = (Y, \mathbf{A}, \mathbf{Z}, S, \mathbf{C})$ and $\eta(\mathbf{O})$ refer to the nuisance parameters (at the truth).

- 1. Split the sample into parts I_k (that are each are of size $n_k = n/K$). Here, K is an integer (we shall assume n is a multiple of K). For each I_k , I_k^c denotes the indices that are not in I_k .
- 2. For each k = 1, ..., k, using I_k^c only, estimate η as $\hat{\eta}_k^c = \hat{\eta}((\mathbf{O}_i)_{i \in I_k^c})$.
- 3. Construct K estimators $\hat{\psi}_k, k = 1, ..., k$ of ψ^{\dagger} : under NEM, solve the equations

$$0 = \sum_{i \in I_k} \phi(\mathbf{Z}_i, S_i, \mathbf{C}_i; \hat{\eta}_k^c) \epsilon_i^*(\psi^{\dagger}, \hat{\eta}_k)$$

for ψ^{\dagger} , for each k = 1, ..., k. Under NSM, solve the equations

$$0 = \begin{pmatrix} \sum_{i \in I_k} \phi(\mathbf{Z}_i, S_i, \mathbf{C}_i; \hat{\eta}_k^c) \epsilon_i^*(\psi^{\dagger}, \hat{\eta}_k^c) \\ \sum_{i \in I_k} S_i \kappa(\mathbf{A}_i, \mathbf{Z}_i, \mathbf{C}_i; \hat{\eta}_k^c) \epsilon_i(\psi^{\dagger}, \hat{\eta}_k^c) \end{pmatrix}$$

for ψ^{\dagger} , for each k = 1, ..., K.

- 4. Take the average of the K estimators of ψ^{\dagger} to obtain $\hat{\psi}_{CF}$.
- 5. Estimate the standard error for the cross-fit estimator of $\hat{\psi}_{CF}$ using a sandwich estimator, as described in Chernozhukov et al. (2018). For example, under NEM,

we estimate the asymptotic variance as $\hat{B}^{-1}\hat{V}(\hat{B}^{-1})^T$, where

$$\hat{V} = \frac{1}{K} \sum_{k=1}^{K} \left[\frac{1}{n_k} \sum_{i \in I_k} \left\{ \phi(\mathbf{Z}_i, S_i, \mathbf{C}_i; \hat{\eta}_k^c) \epsilon_i^*(\hat{\psi}_{CF}, \hat{\eta}_k^c) \right\} \left\{ \phi(\mathbf{Z}_i, S_i, \mathbf{C}_i; \hat{\eta}_k^c) \epsilon_i^*(\hat{\psi}_{CF}, \hat{\eta}_k^c) \right\}^T \right]$$
$$\hat{B} = -\frac{1}{K} \sum_{k=1}^{K} \left[\frac{1}{n_k} \sum_{i \in I_k} \phi(\mathbf{Z}_i, S_i, \mathbf{C}_i; \hat{\eta}_k^c) \epsilon_i^{*'}(\hat{\psi}_{CF}, \hat{\eta}_k^c) \right]$$

and $\epsilon^{*'}(\psi,\eta) = \partial \epsilon^{*}(\psi,\eta)/\partial \psi$ is a row vector that is the length of the the dimension of ψ .

As in other semiparametric regression problems, a complication is how to perform machine-learning based estimation of the nuisance parameters, given that they are not all conditional mean functions that can be estimated directly; see Section 4.2 of Chernozhukov et al. (2018) for further discussion. One option is to restrict to estimation methods that can more easily respect the structure of the semiparametric model (generalised additive models, Lasso, deep neural networks etc); the other is to adopt the 'localised de-biased machine learning' procedure described in Kallus et al. (2019), where e.g. an initial (biased) estimator of ψ^{\dagger} could be used to construct estimators of other nuisance parameters.

A.7 Estimation strategy for ψ^{\dagger} based on parametric working models

- 1. Estimate τ^{\dagger} and α^{\dagger} as $\hat{\tau}$ and $\hat{\alpha}$ using maximum likelihood or M-estimation.
- 2. Estimate ρ^{\dagger} as $\hat{\rho}$ by solving the equations

$$0 = \sum_{i=1}^{n} \left[e_1(\mathbf{Z}_i, \mathbf{C}_i) - \frac{E\{e_1(\mathbf{Z}_i, \mathbf{C}_i)f(S_i = 1 | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \rho^{\dagger})f(S_i = 0 | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \rho^{\dagger}) | \mathbf{C}_i; \hat{\alpha}, \hat{\tau}, \rho^{\dagger}\}}{E\{f(S_i = 1 | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \rho^{\dagger})f(S_i = 0 | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \rho^{\dagger}) | \mathbf{C}_i; \hat{\alpha}, \hat{\tau}, \rho^{\dagger}\}} \right] \times \{S_i - f(S_i = 1 | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \rho^{\dagger})\}$$

for ρ^{\dagger} (Tchetgen Tchetgen et al., 2010), where $e_1(\mathbf{Z}, \mathbf{C})$ is an arbitrary function of

the same dimension of ρ^{\dagger} .

3. Estimate ν^{\dagger} and θ_0^{\dagger} as $\tilde{\nu}$ and $\hat{\theta}_0$ by solving the equations

$$0 = \sum_{i=1}^{n} (1 - S_i) \begin{pmatrix} e_2(\mathbf{Z}_i, \mathbf{C}_i) \\ e_3(\mathbf{C}_i) \end{pmatrix} \epsilon_i^*(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger})$$

for ν^{\dagger} and θ_0^{\dagger} , where $e_2(\mathbf{Z}, \mathbf{C})$ and $e_3(\mathbf{C})$ are of the same dimension as ν^{\dagger} and θ_0^{\dagger} respectively. Re-estimate ν^{\dagger} as $\hat{\nu}$ by solving the equations

$$0 = \sum_{i=1}^{n} (1 - S_i) [e_2(\mathbf{Z}_i, \mathbf{C}_i) - E\{e_2(\mathbf{Z}_i, \mathbf{C}_i) | S_i = 0, \mathbf{C}_i; \hat{\tau}\}] \epsilon_i^*(\psi^{\dagger}, \nu^{\dagger}, \hat{\theta}_0, \theta_1^{\dagger})$$

for ν^{\dagger} (Robins, 1994).

4. Estimate θ_1^{\dagger} and ψ^{\dagger} as $\hat{\theta}_1$ and $\tilde{\psi}$ respectively, by solving the equations

$$0 = \sum_{i=1}^{n} \begin{pmatrix} e_4(\mathbf{C}_i) \{ S_i - E\{S_i | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \hat{\rho} \} \\ e_5(\mathbf{Z}_i, \mathbf{C}_i) \{ S_i - E\{S_i | \mathbf{Z}_i, \mathbf{C}_i; \hat{\alpha}, \hat{\rho} \} \end{pmatrix} \epsilon_i^*(\psi^{\dagger}, \hat{\nu}, \hat{\theta}_0, \theta_1^{\dagger})$$

for θ_1^{\dagger} and ψ^{\dagger} , where $e_4(\mathbf{C}_i)$ and $e_5(\mathbf{Z}_i, \mathbf{C}_i)$ are of the same dimension as θ_1^{\dagger} and ψ^{\dagger} respectively.

5. Re-estimate ψ^{\dagger} as $\hat{\psi}_{MR-NEM}$ by solving the equations

$$0 = \sum_{i=1}^{n} \phi(\mathbf{Z}_{i}, S_{i}, \mathbf{C}_{i}; \hat{\tau}, \hat{\alpha}, \hat{\rho}) \epsilon^{*}(\psi^{\dagger}, \hat{\nu}, \hat{\theta})$$

for ψ^{\dagger} .

In the case that one is interested in inference under the NSM condition, there are additional nuisance parameters to consider. For example, π^{\dagger} can be estimated as $\hat{\pi}$ via maximum likelihood; one can also obtain an estimator $\hat{\omega}$ by solving the equations

$$0 = \sum_{i=1}^{n} e_6(A_i, \mathbf{C}_i) \epsilon_i(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger}, \omega^{\dagger}, \hat{\pi})$$

for ω^{\dagger} . Then $\hat{\psi}_{MR-NSM}$ is obtained by solving the equations

$$0 = \sum_{i=1}^{n} \left(\begin{array}{c} \phi(\mathbf{Z}_{i}, S_{i}, \mathbf{C}_{i}; \hat{\tau}, \hat{\alpha}, \hat{\rho}) \epsilon_{i}^{*}(\psi^{\dagger}, \hat{\nu}, \hat{\theta}) \\ S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \hat{\pi}, \hat{\tau}) \epsilon_{i}(\psi^{\dagger}, \hat{\nu}, \hat{\theta}, \hat{\omega}, \hat{\pi}) \end{array} \right)$$

for ψ^{\dagger} .

A.8 Local semiparametric efficiency

Once we have obtained the class of regular and asymptotically linear estimators of ψ^{\dagger} under a semiparametric model, it remains to identify the optimal estimator within a given class. Under NEM, we are able to compute a closed form representation of the efficient score. Before doing this, we introduce some additional notation. Let us define

$$\mu(\mathbf{Z}, S, \mathbf{C}) = E \left\{ \frac{\partial \beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \psi^{\dagger}) S}{\partial \psi} \Big|_{\psi = \psi^{\dagger}} \Big| \mathbf{Z}, S, \mathbf{C} \right\},$$
$$P_{\sigma}(\mathbf{Z}, \mathbf{C}) = \frac{E\{S\sigma^{-2}(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\}}$$

and $\delta\mu(\mathbf{Z}, \mathbf{C}) = \mu(\mathbf{Z}, 1, \mathbf{C}) - \mu(\mathbf{Z}, 0, \mathbf{C})$, where $\sigma^2(\mathbf{Z}, S, \mathbf{C}) = E\{\epsilon^{*2}(\psi^{\dagger}) | \mathbf{Z}, S, \mathbf{C}\}$.

Theorem A.4. Under the semiparametric model \mathcal{M}_{NEM} and with admissible independence densities

$$f^{\ddagger}(\mathbf{Z}, S|\mathbf{C}) = \left(\frac{1}{2}\right)^{S} \left(\frac{1}{2}\right)^{1-S} f(\mathbf{Z}|\mathbf{C})$$

the optimal index function $r_0^{opt}(\mathbf{Z}, S, \mathbf{C})$ in (8) is

$$r_0^{opt}(\mathbf{Z}, S, \mathbf{C}) = \left\{ \delta\mu(\mathbf{Z}, \mathbf{C}) - \frac{E\left\{\delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\right\}}{E\left\{P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\right\}} \right\} 2(-1)^{1-S}P_{\sigma}(\mathbf{Z}, \mathbf{C}).$$

Furthermore, the efficient score is an unbiased estimating function in the union model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_2 \cup \mathcal{M}_3 \cup \mathcal{M}_4)$ that is locally efficient at the intersection submodel $\mathcal{M}_{NEM} \cap \mathcal{M}_1 \cap \mathcal{M}_2 \cap \mathcal{M}_3 \cap \mathcal{M}_4.$

A proof is given in B.8 of the Appendix. We emphasise that the choice of admissible independence densities is not an assumption on the data generating mechanism. Rather, it allows us to simplify the complex expression for the efficient score given in the Appendix into an equation of the form (8). Similar to the standard instrumental variable set-up, efficient estimation generally requires modelling the conditional mean of **A** given **Z** and **C** in those with S = 1. However, even if this model is misspecified, the resulting estimating of ψ^{\dagger} will remain consistent (although it will no longer generally be efficient). In order to further simplify the above result, we revisit Example 1.

Corollary A.4.1. If **Z** is binary, then the optimal choice $m_{opt}(\mathbf{C})$ of $m(\mathbf{C})$ in the estimating function (9) is

$$m_{opt}(\mathbf{C}) = E\left[\left\{\frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\right\}^2 \sigma^2(\mathbf{Z},S,\mathbf{C}) \left|\mathbf{C}\right]^{-1} \{\mu(Z=1,S=1,\mathbf{C}) - \mu(Z=0,S=1,\mathbf{C})\}.$$

If $\sigma^2(\mathbf{Z}, S, \mathbf{C}) = \sigma^2$, then $m_{opt}(\mathbf{C})$ reduces to $w_0(\mathbf{C})^{-1}\sigma^{-2}\{\mu(Z = 1, S = 1, \mathbf{C}) - \mu(Z = 0, S = 1, \mathbf{C})\}$, where

$$w_0(\mathbf{C}) = \left\{ \frac{1}{f(Z=1, S=1|\mathbf{C})} + \frac{1}{f(Z=1, S=0|\mathbf{C})} + \frac{1}{f(Z=0, S=1|\mathbf{C})} + \frac{1}{f(Z=0, S=0|\mathbf{C})} \right\}$$

Note that the weight function $w_0(\mathbf{C})^{-1}$ will automatically give high weight given in the estimating equations to strata of the data where there is most overlap in terms of the distribution $f(Z, S | \mathbf{C})$. In studies where the inverse weights $1/f(Z, S | \mathbf{C})$ are extreme, we might expect an efficient estimator to thus perform better than other multiply robust estimators both in terms of precision as well as stability and finite sample bias.

A.9 Negative control outcomes - estimation

Let us define (or redefine)

$$q(\mathbf{a}, \mathbf{Z}, \mathbf{C}) = E(Y^{0} | \mathbf{A} = \mathbf{a}, \mathbf{Z}, \mathbf{C}) - E(Y^{0} | \mathbf{A} = \mathbf{0}, \mathbf{Z}, \mathbf{C})$$

$$t(\mathbf{z}, \mathbf{C}) = E(Y^{0} | \mathbf{Z} = \mathbf{z}, \mathbf{C}) - E(Y^{0} | \mathbf{Z} = \mathbf{0}, \mathbf{C})$$

$$b_{1}^{*}(\mathbf{C}) = E(Y^{0} | \mathbf{Z} = \mathbf{0}, \mathbf{C})$$

$$b_{0}(\mathbf{C}) = E(W^{0} | \mathbf{Z} = \mathbf{0}, \mathbf{C}).$$

Under slightly altered versions of Assumptions 8 and 11, $t(\mathbf{z}, \mathbf{C})$ is identified as

$$t(\mathbf{z}, \mathbf{C}) = E(w | \mathbf{Z} = \mathbf{z}, \mathbf{C}) - E(w | \mathbf{Z} = \mathbf{0}, \mathbf{C}).$$

The following result is a corollary of Theorem 3.1.

Corollary A.4.2. The (conditional) density of S is degenerate and $f(\mathbf{Z}|S = 1, \mathbf{C}) = f(\mathbf{Z}|S = 0, \mathbf{C}) = f(\mathbf{Z}|\mathbf{C})$, such that the nuisance tangent space is smaller. Under the semiparametric model implied by restriction (7) and the NEM Assumption 7, the estimating function for ψ^{\dagger} implied by Theorem 3.1 simplifies to

$$[\phi(\mathbf{Z}, \mathbf{C}) - E\{\phi(\mathbf{Z}, \mathbf{C}) | \mathbf{C}\}][Y - W - \beta(\mathbf{A}, \mathbf{C}; \psi^{\dagger}) - \{b_1^*(\mathbf{C}) - b_0(\mathbf{C})\}]$$
(17)

where $\phi(\mathbf{Z}, \mathbf{C})$ is arbitrary. Also, if $q(\mathbf{a}, \mathbf{z}, \mathbf{c}) = q(\mathbf{a}, \mathbf{c})$, then the estimating functions for

 ψ^{\dagger} derived under the NSM Assumption 12 reduce to

$$\begin{pmatrix} [\phi(\mathbf{Z}, \mathbf{C}) - E\{\phi(\mathbf{Z}, \mathbf{C}) | \mathbf{C}\}][Y - W - \beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \psi^{\dagger}) - \{b_{1}^{*}(\mathbf{C}) - b_{0}(\mathbf{C})\}] \\ \kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) \left(Y - \beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \psi^{\dagger}) - [q(\mathbf{A}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\}] - t(\mathbf{Z}, \mathbf{C}) - b_{1}^{*}(\mathbf{C})\right) \end{pmatrix}$$
(18)

where $\phi(\mathbf{Z}, \mathbf{C})$ is arbitrary and $\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C})$ satisfies $E\{\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{A}, \mathbf{C}\} = E\{\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\} = 0.$

With negative control outcomes, following results in Section 3.2 of the main paper, note that estimators of ψ^{\dagger} based on the estimating functions given in Corollary A.4.2 are doubly robust. Specifically, an estimator based on equation (17) is unbiased if either i) $f(\mathbf{Z}|\mathbf{C})$ or ii) $b_1^*(\mathbf{C})$ and $b_0(\mathbf{C})$ (or their difference) are consistently estimated. Similarly, an estimator based on equation (18) is unbiased if, in addition to $f(\mathbf{A}|\mathbf{Z},\mathbf{C})$, either i) $f(\mathbf{Z}|\mathbf{C})$ or ii) $q(\mathbf{A},\mathbf{C})$, $t(\mathbf{Z},\mathbf{C})$ $b_1^*(\mathbf{C})$ and $b_0(\mathbf{C})$ are consistently estimated. Hence, with a valid negative control outcome, our estimators are expected to be additionally robust and efficient relative to estimators with a valid reference population.

A.10 The average treatment effect in the treated

It may be that interest is in the marginal rather than the conditional ATT. Suppose that **A** and **Z** are binary; then in the case that $\beta(Z) = \beta$, previous methods can be used due to the collapsibility of the linear link function, but one may not wish to invoke this restriction. It follows from the identification results in Section 2 that under the NEM Assumption 5,

$$\psi^* = E(Y^1 - Y^0 | A = 1, S = 1) = E\{E(Y^1 - Y^0 | A = 1, Z, S = 1, \mathbf{C}) | A = 1, S = 1\}$$

is identified as

$$\psi^* = \int \beta(\mathbf{c}) dF(\mathbf{c}|A=1,S=1)$$

where

$$\beta(\mathbf{C}) = \frac{\delta^{Y}(\mathbf{C}) - t(1, \mathbf{C})}{\delta^{A}(\mathbf{C})}$$

$$\delta^{Y}(\mathbf{C}) = E(Y|Z = 1, S = 1, \mathbf{C}) - E(Y|Z = 0, S = 1, \mathbf{C})$$

$$\delta^{A}(\mathbf{C}) = f(A = 1|Z = 1, S = 1, \mathbf{C}) - f(A = 1|Z = 0, S = 1, \mathbf{C}).$$

We therefore have a closed form representation of ψ^* as a functional of the observed data distribution, Since ψ^* is a pathwise differentiable parameter, we can then obtain nonparametric inference on ψ , by obtaining the efficient influence function under a nonparametric model. The following results may be of independent interest with respect to the literature of nonparametric inference in the IV model (Wang and Tchetgen Tchetgen, 2018).

Theorem A.5. In the nonparametric model defined by Assumptions 2-5, the efficient influence function is equal to:

$$EIF_{1}(\psi^{*}) = \frac{f(A = 1, S = 1 | \mathbf{C})(-1)^{Z+S}}{f(A = 1, S = 1)\delta^{A}(\mathbf{C})f(Z, S | \mathbf{C})}$$

$$\times [Y - \beta(\mathbf{C})\{A - f(A = 1 | Z = 0, S = 1, \mathbf{C})\}S - t(1, \mathbf{C})Z - E(Y | Z = 0, S, \mathbf{C})]$$

$$+ \frac{1}{f(A = 1, S = 1)}AS\{\beta(\mathbf{C}) - \psi^{*}\}.$$

A proof can be found in section B.9. One can use these results to create estimators of ψ^* , after obtaining estimates of the nuisance parameters involved.

B Proofs

B.1 Proof of Proposition 2.0.1

Proof. For any $z \in \{0, 1\}$ and $\mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$,

$$E(Y|Z = z, S = 0, \mathbf{C} = \mathbf{c}) = E(Y^0|Z = z, S = 0, \mathbf{C} = \mathbf{c})$$
(Assumption 1)
$$= E(Y^{0,z}|Z = z, S = 0, \mathbf{C} = \mathbf{c})$$
(Instrument consistency)
$$= E(Y^{0,z}|S = 0, \mathbf{C} = \mathbf{c})$$
(Unconfoundedness)
$$= E(Y^0|S = 0, \mathbf{C} = \mathbf{c})$$
(Exclusion restriction)

where $E(Y^0|S = 0, \mathbf{C} = \mathbf{c})$ is not a function of z.

B.2 Proof of Theorem 2.1

Proof. Note that $\forall z \in \{0,1\}$ and $\forall \mathbf{c} \in \mathcal{C}_0 \cap \mathcal{C}_1$

$$E(Y|A = a, z, S = 1, \mathbf{c}) = \beta(a, z, \mathbf{c}) + \gamma(z, \mathbf{c})\{a - f(A = 1|z, S = 1, \mathbf{c})\}$$
$$+ t(z, \mathbf{c}) + E(Y^0|Z = 0, S = 1, \mathbf{c})$$

(Tchetgen Tchetgen and Vansteelandt, 2013). To obtain identification, the right hand side must be reduced by two parameters.

First,

$$t(z, \mathbf{c}) = E(Y^0 | Z = 1, S = 0, \mathbf{C} = \mathbf{c}) - E(Y^0 | Z = 0, S = 0, \mathbf{C} = \mathbf{c})$$
(Assumption 4)
= $E(Y | Z = 1, S = 0, \mathbf{C} = \mathbf{c}) - E(Y | Z = 0, S = 0, \mathbf{C} = \mathbf{c}).$ (Assumption 1)

Then we have

$$\begin{split} &E(Y|A = a, z, S = 1, \mathbf{c}) \\ &= \beta(a, z, \mathbf{c}) + \gamma(z, \mathbf{c}) \{ a - f(A = 1 | z, S = 1, \mathbf{c}) \} \\ &+ E(Y|Z = z, S = 0, \mathbf{C} = \mathbf{c}) - E(Y|Z = 0, S = 0, \mathbf{C} = \mathbf{c}) + E(Y^0|Z = 0, S = 1, \mathbf{c}). \end{split}$$

Then either NEM or NSM can be applied to remove a further degree-of-freedom. The remaining results follow via rearranging the above formula as an expression for $\beta(1, z, \mathbf{c})$; see also the Appendix of Richardson and Tchetgen Tchetgen (2021) where the second result (under NEM) is shown.

B.3 Proof of Theorem 3.1

Proof. We introduce some additional notation:

$$\epsilon_{1} = Y - \beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - [q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}] - b_{1}^{*}(\mathbf{C}) - t(\mathbf{Z}, \mathbf{C})$$

$$\epsilon_{1}^{*} = \epsilon_{1} + [q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}]$$

$$\epsilon_{0} = Y - b_{0}(\mathbf{C}) - t(\mathbf{Z}, \mathbf{C})$$

where $b_1^*(\mathbf{C}) = b_1(\mathbf{C}) + b_0(\mathbf{C})$. Note that in order to obtain identification, we enforce that $\beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}) = \beta(\mathbf{A}, \mathbf{C})$.

The likelihood for a given observation can be written as

$$f(\mathbf{O}) = f(\epsilon_0 | \mathbf{Z}, S = 0, \mathbf{C})^{(1-S)} \{ f(\epsilon_1 | \mathbf{A}, \mathbf{Z}, S = 1, \mathbf{C}) f(\mathbf{A} | \mathbf{Z}, S = 1, \mathbf{C}) \}^S f(\mathbf{Z}, S | \mathbf{C}) f(\mathbf{C}).$$

Then we will consider the parametric submodel:

$$f_r(\mathbf{O}) = f_r(\epsilon_{0_r} | \mathbf{Z}, S = 0, \mathbf{C})^{(1-S)} \{ f_r(\epsilon_{1_r} | \mathbf{A}, \mathbf{Z}, S = 1, \mathbf{C}) f_r(A | \mathbf{Z}, S = 1, \mathbf{C}) \}^S f_r(\mathbf{Z}, S | \mathbf{C}) f_r(S, \mathbf{C})$$

which varies in the direction of $q_r(A, \mathbf{Z})$, $b_{0_r}(\mathbf{C})$, $b_{1_r}^*(\mathbf{C})$, $t_r(\mathbf{Z})$, $f_r(\mathbf{A}|\mathbf{Z}, S = 1, \mathbf{C})$, $f_r(\mathbf{Z}, S|\mathbf{C})$ and $f_r(\mathbf{C})$. Here,

$$\epsilon_{1_r} = Y - \beta(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - [q_r(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E_r \{q_r(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}] - b_{1_r}^*(\mathbf{C}) - t_r(\mathbf{Z}, \mathbf{C})$$

$$\epsilon_{0_r} = Y - b_{0_r}(\mathbf{C}) - t_r(\mathbf{Z}, \mathbf{C}).$$

The nuisance tangent space λ_{nuis} under \mathcal{M}_{NEM} can be characterised as

$$\lambda_{nuis} = \lambda_{nuis_1} \oplus \lambda_{nuis_2} \oplus \lambda_{nuis_3} \oplus \lambda_{nuis_4} \oplus \lambda_{nuis_5} \oplus \lambda_{nuis_6} \oplus \lambda_{nuis_7} \oplus \lambda_{nuis_8} \oplus \lambda_{nuis_9}$$

where

$$\begin{split} \Lambda_{nuis_{1}} &= \left\{ Sd_{1}(\epsilon_{1},\mathbf{A},\mathbf{Z},\mathbf{C}) : \\ &= E\{d_{1}(\epsilon_{1},\mathbf{A},\mathbf{Z},\mathbf{C})|\mathbf{A},\mathbf{Z},S=1,\mathbf{C}\} = E\{\epsilon_{1}d_{1}(\epsilon_{1},\mathbf{A},\mathbf{Z},\mathbf{C})|\mathbf{A},\mathbf{Z},S=1,\mathbf{C}\} = 0 \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{2}} &= \left\{ (1-S)d_{2}(\epsilon_{0},\mathbf{Z},\mathbf{C}) : E\{d_{2}(\epsilon_{0},\mathbf{Z},\mathbf{C})|\mathbf{Z},S=0,\mathbf{C}\} = E\{\epsilon_{0}d_{2}(\epsilon_{1},\mathbf{Z})|\mathbf{Z},S=0,\mathbf{C}\} = 0 \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{3}} &= \left\{ d_{3}(\mathbf{Z},S,\mathbf{C}) : E\{d_{3}(\mathbf{Z},S,\mathbf{C})|\mathbf{C}\} = 0 \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{4}} &= \left\{ d_{4}(\mathbf{C}) : E\{d_{4}(\mathbf{C})\} = 0 \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{5}} &= \left\{ S[d_{5}(\mathbf{A},\mathbf{Z},\mathbf{C}) - E\{d_{5}(\mathbf{A},\mathbf{Z},\mathbf{C})|\mathbf{Z},S=1,\mathbf{C}\}]f_{\epsilon_{1}}' : d_{5}(\mathbf{A},\mathbf{Z},\mathbf{C}) \text{ unrestricted} \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{6}} &= \left\{ Sd_{6}(A,\mathbf{Z},\mathbf{C}) + Sf_{\epsilon_{1}}' \int d_{6}(A^{*},\mathbf{Z},\mathbf{C})q(A^{*},\mathbf{Z},\mathbf{C})dF(A^{*}|\mathbf{Z},S=1,\mathbf{C}) : \\ &= E\{d_{6}(A,\mathbf{Z},\mathbf{C})|\mathbf{Z},S=1,\mathbf{C}\} = 0 \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{7}} &= \left\{ Sd_{7}(\mathbf{C})f_{\epsilon_{1}}' : d_{7}(\mathbf{C}) \text{ unrestricted} \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{8}} &= \left\{ (1-S)d_{8}(\mathbf{C})f_{\epsilon_{0}}' : d_{8}(\mathbf{C}) \text{ unrestricted} \right\} \cap L_{2}^{0} \\ \Lambda_{nuis_{9}} &= \left\{ Sd_{9}(\mathbf{Z},\mathbf{C})f_{\epsilon_{1}}' + (1-S)d_{9}(\mathbf{Z},\mathbf{C})f_{\epsilon_{0}}' : d_{9}(\mathbf{C}) \text{ unrestricted} \right\} \cap L_{2}^{0} \\ \end{split}$$

where f'_{ϵ_1} is the derivative of $f(\epsilon_1 | A, \mathbf{Z}, S = 1, \mathbf{C})$ w.r.t. ϵ_1 and likewise f'_{ϵ_0} is the derivative of $f(\epsilon_0 | \mathbf{Z}, S = 0, \mathbf{C})$ w.r.t. ϵ_0 .

Using standard results on the restricted mean model e.g. Tsiatis (2007), we have that

$$\Lambda_{nuis_1}^{\perp} \cap \Lambda_{nuis_3}^{\perp} \cap \Lambda_{nuis_4}^{\perp} = \left\{ S\epsilon_1 c_1(\mathbf{A}, \mathbf{Z}, \mathbf{C}) + Sc_2(\mathbf{A}, \mathbf{Z}, \mathbf{C}) : \\ c_1(\mathbf{A}, \mathbf{Z}, \mathbf{C}) \text{ unrestricted}, E\{c_2(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\} = 0 \right\} \cap L_2^0$$

Then to find elements in this space that are orthogonal to Λ_{nuis_5} , we must find the elements in $\Lambda_{nuis_1}^{\perp} \cap \Lambda_{nuis_3}^{\perp} \cap \Lambda_{nuis_4}^{\perp}$ that satisfy:

$$0 = E \left(S\{\epsilon_1 c_1(\mathbf{A}, \mathbf{Z}, \mathbf{C}) + c_2(\mathbf{A}, \mathbf{Z}, \mathbf{C}) \} [d_5(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{d_5(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}] f'_{\epsilon_1} \right)$$

= $E \left(Sc_1(\mathbf{A}, \mathbf{Z}, \mathbf{C}) [d_5(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{d_5(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}] \right).$

It follows that elements of $Sc_1(\mathbf{A}, \mathbf{Z}, \mathbf{C})$ that will satisfy the equality are of the form $S\phi_1(\mathbf{Z}, \mathbf{C})$, where $\phi_1(\mathbf{Z}, \mathbf{C})$ are unrestricted. One can also show that the elements

$$S\epsilon_1[\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C})|S=1, \mathbf{C}\}] + Sc_2(\mathbf{A}, \mathbf{Z}, \mathbf{C})$$

are orthogonal to Λ_{nuis_7} .

Next, in considering Λ_{nuis_6} , we need elements that satisfy:

$$0 = E \left\{ S\left(\epsilon_1[\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}\right] + c_2(\mathbf{A}, \mathbf{Z}, \mathbf{C})\right) \times \left[d_6(A, \mathbf{Z}, \mathbf{C}) - E\{Sd_6(A, \mathbf{Z}, \mathbf{C})q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}\right] f_{\epsilon_1}' \right\}$$

Then note that

$$E\left\{S\epsilon_{1}[\phi_{1}(\mathbf{Z},\mathbf{C}) - E\{\phi_{1}(\mathbf{Z},\mathbf{C})|S=1,\mathbf{C}\}]d_{6}(\mathbf{A},\mathbf{Z},\mathbf{C})\right\} = 0$$
$$E\left\{-Sc_{2}(\mathbf{A},\mathbf{Z},\mathbf{C})E\{d_{6}(A,\mathbf{Z},\mathbf{C})q(\mathbf{A},\mathbf{Z},\mathbf{C})|\mathbf{Z},S=1,\mathbf{C}\}f_{\epsilon_{1}}'\right\} = 0$$

We are left with the restriction that

$$0 = E\left(Sc_2(\mathbf{A}, \mathbf{Z}, \mathbf{C})d_6(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - S\epsilon_1[\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C})|S = 1, \mathbf{C}\}]E\{d_6(A, \mathbf{Z}, \mathbf{C})q(\mathbf{A}, \mathbf{Z}, \mathbf{C})|\mathbf{Z}, S = 1, \mathbf{C}\}f'_{\epsilon_1}\right)$$

$$= E\left(Sd_6(\mathbf{A}, \mathbf{Z}, \mathbf{C}) + [\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C})|S = 1, \mathbf{C}\}][q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C})|\mathbf{Z}, S = 1, \mathbf{C}\}]\right)$$

and so

$$c_{2}(\mathbf{A}, \mathbf{Z}, \mathbf{C}) = [\phi_{1}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{1}(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}][q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}]$$

Hence, so far we have shown that

$$\Lambda_{nuis_1}^{\perp} \cap \Lambda_{nuis_3}^{\perp} \cap \Lambda_{nuis_4}^{\perp} \cap \Lambda_{nuis_5}^{\perp} \cap \Lambda_{nuis_6}^{\perp} \cap \Lambda_{nuis_7}^{\perp} = \left\{ S\epsilon_1^* [\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}] : \phi_1(\mathbf{Z}, \mathbf{C}) \text{ unrestricted} \right\} \cap L_2^0$$

Considering elements in $\Lambda_{nuis_2}^{\perp} \cap \Lambda_{nuis_8}^{\perp}$, then using previous reasoning, we have that

$$\Lambda_{nuis_2}^{\perp} \cap \Lambda_{nuis_8}^{\perp} = \{ (1-S)\epsilon_0 [\phi_2(\mathbf{Z}, \mathbf{C}) - E\{\phi_2(\mathbf{Z}, \mathbf{C}) | \mathbf{C}, S = 0\}]; \phi_2(\mathbf{Z}, \mathbf{C}) \text{ unrestricted} \}$$

It is also straightforward to show that elements in the space $\Lambda_{nuis_2}^{\perp} \cap \Lambda_{nuis_8}^{\perp}$ are orthogonal

to those in the space $\Lambda_{nuis_1}^{\perp} \cap \Lambda_{nuis_3}^{\perp} \cap \Lambda_{nuis_4}^{\perp} \cap \Lambda_{nuis_5}^{\perp} \cap \Lambda_{nuis_6}^{\perp} \cap \Lambda_{nuis_7}^{\perp}$, and therefore

$$\begin{split} \Lambda_{nuis_1}^{\perp} \cap \Lambda_{nuis_2}^{\perp} \cap \Lambda_{nuis_3}^{\perp} \cap \Lambda_{nuis_4}^{\perp} \cap \Lambda_{nuis_5}^{\perp} \cap \Lambda_{nuis_6}^{\perp} \cap \Lambda_{nuis_7}^{\perp} \cap \Lambda_{nuis_8}^{\perp} \\ &= \bigg\{ S\epsilon_1^* [\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}] \\ &+ (1 - S)\epsilon_0 [\phi_2(\mathbf{Z}, \mathbf{C}) - E\{\phi_2(\mathbf{Z}, \mathbf{C}) | \mathbf{C}, S = 0\}] : \phi_1(\mathbf{Z}, \mathbf{C}), \phi_2(\mathbf{Z}, \mathbf{C}) \ unrestricted \bigg\}. \end{split}$$

It remains to find elements in this space that are orthogonal to $\Lambda_{nuis_9}^{\perp}$; these must satisfy

$$0 = E \left\{ \left(S\epsilon_{1}^{*} [\phi_{1}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{1}(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\} \right] + (1 - S)\epsilon_{0} [\phi_{2}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{2}(\mathbf{Z}, \mathbf{C}) | S = 0, \mathbf{C}\}] \right) \\ \times \{Sd_{9}(\mathbf{Z}, \mathbf{C})f_{\epsilon_{1}}' + (1 - S)d_{9}(\mathbf{Z}, \mathbf{C})f_{\epsilon_{0}}'\} \right) \\ = E \left\{ \left(S[\phi_{1}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{1}(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\} \right] + (1 - S)[\phi_{2}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{2}(\mathbf{Z}, \mathbf{C}) | S = 0, \mathbf{C}\}] \right) d_{9}(\mathbf{Z}, \mathbf{C}) \right\}$$

It follows from Tchetgen Tchetgen et al. (2010) that the space of elements

$$S[\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}] + (1 - S)[\phi_2(\mathbf{Z}, \mathbf{C}) - E\{\phi_2(\mathbf{Z}, \mathbf{C}) | \mathbf{C}, S = 0\}]$$

that satisfy this equality can be represented as

$$\Omega = \{\phi(\mathbf{Z}, S, \mathbf{C}) : E\{\phi(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\} = E\{\phi(\mathbf{Z}, S, \mathbf{C}) | S, \mathbf{C}\} = 0\}.$$

Then the main result follows.

B.4 Proof of Theorem 3.2

Proof. We will first show that

$$E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\epsilon^{*}(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger})\}$$

evaluated at the limiting (rather than estimated) values is an unbiased estimating function under the union model. Under model $\mathcal{M}_{NEM} \cap \mathcal{M}_1$, by the law of iterated expectation,

$$E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\epsilon^{*}(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger})\}$$

$$= E\left(\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})[b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta^{\dagger}_{0}) - b_{1}(\mathbf{C}; \theta^{\dagger}_{1})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}) + q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}]\right)$$

$$= E\left[\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta^{\dagger}_{0}) - b_{1}(\mathbf{C}; \theta^{\dagger}_{1})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right] = 0$$

Under model $\mathcal{M}_{NEM} \cap \mathcal{M}_2$, looking back to the final line of the previous expression,

$$E\left[\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right]$$

$$= E\left[\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S\}\right]$$

$$= E\left[E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})|S, \mathbf{C}\}\{b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S\}\right] = 0$$

where the final equality follows since $f(\mathbf{Z}|S, \mathbf{C}) = f(\mathbf{Z}|S, \mathbf{C}; \nu^{\dagger}, \rho^{\dagger})$.

Under model $\mathcal{M}_{NEM} \cap \mathcal{M}_3$,

$$E\left[\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right]$$
$$= E\left[E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})|\mathbf{Z}, \mathbf{C}\}\{b_{0}(\mathbf{C}) + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right] = 0$$

where the final equality follows since $f(S|S, \mathbf{Z}, \mathbf{C}) = f(S|\mathbf{Z}, \mathbf{C}; \alpha^{\dagger}, \rho^{\dagger}).$

Finally, under model $\mathcal{M}_{NEM} \cap \mathcal{M}_4$,

$$E\left[\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right]$$

$$= E\left[E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})|S, \mathbf{C}\}\{b_{1}(\mathbf{C})S - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S\}\right]$$

$$+ E\left[E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})|\mathbf{Z}, \mathbf{C}\}\{t(\mathbf{Z}, \mathbf{C}) - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right]$$

$$+ E\left\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger})\}\right\} = 0.$$

Note furthermore that

- $f(\mathbf{Z}|S, \mathbf{C}; \hat{\tau}, \hat{\rho})$ is a CAN estimator of $f(\mathbf{Z}|S, \mathbf{C})$ in model $\mathcal{M}_2 \cup \mathcal{M}_4$.
- $f(S|\mathbf{Z}, \mathbf{C}; \hat{\alpha}, \hat{\rho})$ is a CAN estimator of $f(S|\mathbf{Z}, \mathbf{C})$ in model $\mathcal{M}_3 \cup \mathcal{M}_4$.
- $t(\mathbf{Z}, \mathbf{C}; \hat{\nu})$ is a CAN estimator of $t(\mathbf{Z}, \mathbf{C})$ in model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_2)$.
- $b_1(\mathbf{C}; \hat{\theta}_1)$ is a CAN estimator of $b_1(\mathbf{C})$ in model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_3)$.
- $b_0(\mathbf{C}; \hat{\theta}_0)$ is a CAN estimator of $b_0(\mathbf{C})$ in model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_2 \cup \mathcal{M}_3)$.

These results follow from Robins et al. (1992) and Tchetgen Tchetgen et al. (2010). This completes the proof. $\hfill \Box$

B.5 Proof of Theorem A.1

Proof. The conditional mean $E(Y|A = a, Z = z, S = 1, \mathbf{C} = \mathbf{c})$ is equal to

$$E(Y|A = a, z, S = 1, \mathbf{c})$$

= $E(Y^1 - Y^0|A = 1, z, S = 1, \mathbf{c})a$
+ $\gamma(z, \mathbf{c})\{a - Pr(A = 1|z, S = 1, \mathbf{c})\}$
+ $t(z, \mathbf{c}) + E(Y^0|Z = 0, S = 1, \mathbf{c}).$

Note that

$$E(Y^{1} - Y^{0}|A = 1, Z = z, S = 1, \mathbf{C} = \mathbf{c}) = 0$$
 (Under (14))
$$E(Y|Z = z, S = 0, \mathbf{c}) - E(Y|Z = 0, S = 0, \mathbf{c}) = t(z, \mathbf{c})$$
 (Assumptions 1 - 4)

Then after recentering Y and averaging over A,

$$E\{Y - E(Y|Z = z, S = 0, \mathbf{c}) + E(Y|Z = 0, S = 0, \mathbf{c})|z, S = 1, \mathbf{c}\}$$
$$= E(Y^0|Z = 0, S = 1, \mathbf{c})$$

which is not a function of z.

B.6 Proof of Theorem A.2

Proof. Many of the steps in in this proof follow along the lines of the previous proof and can therefore be omitted for brevity. We note however that NSM Assumption (12) imposes different restrictions on the nuisance tangent space, such that we redefine Λ_{nuis_5} as

$$\Lambda_{nuis_5} = \left\{ S[d_5(\mathbf{A}, \mathbf{C}) - E\{d_5(\mathbf{A}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}] f'_{\epsilon_1} : d_5(\mathbf{A}, \mathbf{C}) \text{ unrestricted} \right\} \cap L^0_2.$$

Along the lines of the proof of Theorem 4 in Tchetgen Tchetgen and Vansteelandt

(2013), one can show that

$$\begin{split} \Lambda_{nuis_1}^{\perp} \cap \Lambda_{nuis_3}^{\perp} \cap \Lambda_{nuis_4}^{\perp} \cap \Lambda_{nuis_5}^{\perp} \cap \Lambda_{nuis_6}^{\perp} \cap \Lambda_{nuis_7}^{\perp} \\ &= \left\{ S\epsilon_1[\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) + \phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}] \\ &+ S[q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) | \mathbf{Z}, S = 1, \mathbf{C}\}][\phi_1(\mathbf{Z}, \mathbf{C}) - E\{\phi_1(\mathbf{Z}, \mathbf{C}) | S = 1, \mathbf{C}\}] \\ &\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) \in \Gamma, \ \phi_1(\mathbf{Z}, \mathbf{C}) \ unrestricted \right\} \cap L_2^0 \end{split}$$

and as in the previous proof,

$$\Lambda_{nuis_2}^{\perp} \cap \Lambda_{nuis_8}^{\perp} = \{ (1-S)\epsilon_0[\phi_2(\mathbf{Z}, \mathbf{C}) - E\{\phi_2(\mathbf{Z}, \mathbf{C}) | \mathbf{C}, S=0\}] : \phi_2(\mathbf{Z}, \mathbf{C}) \text{ unrestricted} \}$$

Then one can find the elements

$$S\epsilon_{1}[\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}) + \phi_{1}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{1}(\mathbf{Z}, \mathbf{C})|S = 1, \mathbf{C}\}]$$

+ $[q(\mathbf{A}, \mathbf{Z}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{Z}, \mathbf{C})|\mathbf{Z}, S = 1, \mathbf{C}\}][\phi_{1}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{1}(\mathbf{Z}, \mathbf{C})|S = 1, \mathbf{C}\}]$
+ $(1 - S)\epsilon_{0}[\phi_{2}(\mathbf{Z}, \mathbf{C}) - E\{\phi_{2}(\mathbf{Z}, \mathbf{C})|\mathbf{C}, S = 0\}]$

that are orthogonal to λ_{nuis_9} as in the previous proof, and the main result follows.

B.7 Proof of Theorem A.3

Proof. If we consider the estimating function

$$S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})\epsilon(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger}, \omega^{\dagger}, \pi^{\dagger}) + \phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\epsilon^{*}(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger})$$

then it follows from the previous proof that

$$E\{\phi(\mathbf{Z}, S, \mathbf{C}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger})\epsilon^{*}(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger})\} = 0$$

under the union model.

Under model $\mathcal{M}_{NSM} \cap \mathcal{M}_a \cap \mathcal{M}_{1q}$,

$$E\{S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})\epsilon(\psi^{\dagger}, \nu^{\dagger}, \theta^{\dagger}, \omega^{\dagger}, \pi^{\dagger})\}$$

= $E\left(S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})[b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta^{\dagger}_{0}) - b_{1}(\mathbf{C}; \theta^{\dagger}_{1})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}) + q(\mathbf{A}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{C})|\mathbf{Z}, S = 1, \mathbf{C}\} - q(\mathbf{A}, \mathbf{C}; \omega^{\dagger}) + E\{q(\mathbf{A}, \mathbf{C}; \omega^{\dagger})|\mathbf{Z}, S = 1, \mathbf{C}; \pi^{\dagger}\}]\right) = 0$

Under model $\mathcal{M}_{NSM} \cap \mathcal{M}_a \cap \mathcal{M}_2$,

$$\begin{split} &E\bigg(S\kappa(\mathbf{A},\mathbf{Z},\mathbf{C};\pi^{\dagger},\tau^{\dagger},\rho^{\dagger})[b_{0}(\mathbf{C})+b_{1}(\mathbf{C})S+t(\mathbf{Z},\mathbf{C})-b_{0}(\mathbf{C};\theta^{\dagger}_{0})-b_{1}(\mathbf{C};\theta^{\dagger}_{1})S-t(\mathbf{Z},\mathbf{C};\nu^{\dagger})\\ &+q(\mathbf{A},\mathbf{C})-E\{q(\mathbf{A},\mathbf{C})|\mathbf{Z},S=1,\mathbf{C}\}-q(\mathbf{A},\mathbf{C};\omega^{\dagger})+E\{q(\mathbf{A},\mathbf{C};\omega^{\dagger})|\mathbf{Z},S=1,\mathbf{C};\pi^{\dagger}\}]\bigg)\\ &=E\bigg(S\kappa(\mathbf{A},\mathbf{Z},\mathbf{C};\pi^{\dagger},\tau^{\dagger},\rho^{\dagger})[b_{0}(\mathbf{C})+b_{1}(\mathbf{C})S-b_{0}(\mathbf{C};\theta^{\dagger}_{0})-b_{1}(\mathbf{C};\theta^{\dagger}_{1})S-\\ &+q(\mathbf{A},\mathbf{C})-E\{q(\mathbf{A},\mathbf{C})|\mathbf{Z},S=1,\mathbf{C}\}-q(\mathbf{A},\mathbf{C};\omega^{\dagger})+E\{q(\mathbf{A},\mathbf{C};\omega^{\dagger})|\mathbf{Z},S=1,\mathbf{C};\pi^{\dagger}\}]\bigg)\\ &=E\bigg[SE\{\kappa(\mathbf{A},\mathbf{Z},\mathbf{C};\pi^{\dagger},\tau^{\dagger},\rho^{\dagger})|S=1,\mathbf{C}\}\{b_{0}(\mathbf{C})+b_{1}(\mathbf{C})S-b_{0}(\mathbf{C};\theta^{\dagger}_{0})-b_{1}(\mathbf{C};\theta^{\dagger}_{1})S\}\bigg]\\ &+E\big[SE\{\kappa(\mathbf{A},\mathbf{Z},\mathbf{C};\pi^{\dagger},\tau^{\dagger},\rho^{\dagger})|\mathbf{A},S=1,\mathbf{C}\}\{q(\mathbf{A},\mathbf{C})-q(\mathbf{A},\mathbf{C};\omega^{\dagger})\}\big]\\ &-E\bigg(SE\{\kappa(\mathbf{A},\mathbf{Z},\mathbf{C};\pi^{\dagger},\tau^{\dagger},\rho^{\dagger})|\mathbf{Z},S=1,\mathbf{C}\}[E\{q(\mathbf{A},\mathbf{C})|\mathbf{Z},S=1,\mathbf{C}\}\\ &-E\{q(\mathbf{A},\mathbf{C};\omega^{\dagger})|\mathbf{Z},S=1,\mathbf{C};\pi^{\dagger}\}]\bigg)\\ &=0\end{split}$$

where the final equality follows since $f(\mathbf{A}, \mathbf{Z}|S = 1, \mathbf{C}) = f(\mathbf{A}, \mathbf{Z}|S = 1, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger}).$

Under model $\mathcal{M}_{NSM} \cap \mathcal{M}_a \cap \mathcal{M}_{3q}$,

$$E\left(S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})[b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}) + q(\mathbf{A}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{C})|\mathbf{Z}, S = 1, \mathbf{C}\} - q(\mathbf{A}, \mathbf{C}; \omega^{\dagger}) + E\{q(\mathbf{A}, \mathbf{C}; \omega^{\dagger})|\mathbf{Z}, S = 1, \mathbf{C}; \pi^{\dagger}\}]\right)$$

$$= E\left[S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})\{b_{0}(\mathbf{C}) + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right]$$

$$= E\left[SE\{\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})|\mathbf{Z}, S = 1, \mathbf{C}\}\{b_{0}(\mathbf{C}) + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger})\}\right]$$

$$= 0$$

where the final equality follows since $f(\mathbf{A}|, \mathbf{Z}, S = 1, \mathbf{C}) = f(\mathbf{A}|\mathbf{Z}, S = 1, \mathbf{C}; \pi^{\dagger})$.

Under model $\mathcal{M}_{NSM} \cap \mathcal{M}_a \cap \mathcal{M}_4$, it follows from previous arguments that

$$E\left(S\kappa(\mathbf{A}, \mathbf{Z}, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}, \rho^{\dagger})[b_{0}(\mathbf{C}) + b_{1}(\mathbf{C})S + t(\mathbf{Z}, \mathbf{C}) - b_{0}(\mathbf{C}; \theta_{0}^{\dagger}) - b_{1}(\mathbf{C}; \theta_{1}^{\dagger})S - t(\mathbf{Z}, \mathbf{C}; \nu^{\dagger}) + q(\mathbf{A}, \mathbf{C}) - E\{q(\mathbf{A}, \mathbf{C})|\mathbf{Z}, S = 1, \mathbf{C}\} - q(\mathbf{A}, \mathbf{C}; \omega^{\dagger}) + E\{q(\mathbf{A}, \mathbf{C}; \omega^{\dagger})|\mathbf{Z}, S = 1, \mathbf{C}; \pi^{\dagger}\}]\right) = 0$$

since $f(\mathbf{A}, \mathbf{Z}|S = 1, \mathbf{C}) = f(\mathbf{A}, \mathbf{Z}|S = 1, \mathbf{C}; \pi^{\dagger}, \tau^{\dagger}).$

B.8 Proof of Theorem A.4

Proof. Under a restricted moment model where $t(\mathbf{Z}, \mathbf{C})$, $b_0(\mathbf{C})$, $b_1(\mathbf{C})$ and $q(\mathbf{A}, \mathbf{Z}, \mathbf{C})$ are known, it follows e.g. from Robins (1994) that the efficient score for ψ^{\dagger} is equal to

$$U_{RM-eff} = \mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\epsilon^*(\psi^{\dagger}).$$

It also follows from the proofs of Theorem 1 and 4 in Vansteelandt et al. (2008) that the nuisance tangent space under \mathcal{M}_{NEM} obtained in Theorem 3.1 can be equivalently represented as

$$\left\{ \{e_0(\mathbf{C}) + e_1(S, \mathbf{C}) + e_2(\mathbf{Z}, \mathbf{C})\} \sigma^{-2}(\mathbf{Z}, S, \mathbf{C}) \epsilon^*(\psi^{\dagger}) : e_0 \in \mathcal{C}_0, e_1 \in \mathcal{C}_1, e_2 \in \mathcal{C}_2 \right\} \cap L_2^0$$

where $C_0 = \{e_0(\mathbf{C})\} \cap \mathcal{H}, C_1 = \{e_1(S, \mathbf{C})\} \cap \mathcal{H}, C_2 = \{e_2(\mathbf{Z}, \mathbf{C})\} \cap \mathcal{H} \text{ and } \mathcal{H} \text{ is the Hilbert}$ space of functions of $\mathbf{Z}, S, \mathbf{C}$ with inner product given by $E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})e_1(\mathbf{Z}, S, \mathbf{C})e_2(\mathbf{Z}, S, \mathbf{C})\}$ for all e_1, e_2 .

Then the efficient score under model \mathcal{M}_{NEM} is equal to the following projection

$$\Pi_{L_{2}^{0}}\left(U_{RM-eff}|[\{e_{0}(\mathbf{C})+e_{1}(S,\mathbf{C})+e_{2}(\mathbf{Z},\mathbf{C})\}\sigma^{-2}(\mathbf{Z},S,\mathbf{C})\epsilon^{*}(\psi^{\dagger})]^{\perp}:e_{0}\in\mathcal{C}_{0},e_{1}\in\mathcal{C}_{1},e_{2}\in\mathcal{C}_{2}\right)$$
$$\Pi_{\mathcal{H}}\left(\mu(\mathbf{Z},S,\mathbf{C})|\{e_{0}(\mathbf{C})+e_{1}(S,\mathbf{C})+e_{2}(\mathbf{Z},\mathbf{C})\}^{\perp}:e_{0}\in\mathcal{C}_{0},e_{1}\in\mathcal{C}_{1},e_{2}\in\mathcal{C}_{2}\right)\sigma^{-2}(\mathbf{Z},S,\mathbf{C})\epsilon^{*}(\psi^{\dagger})$$

where $\Pi_{L_2^0}(\cdot|\cdot)$ is the orthogonal projection operator in L_2^0 , and $\Pi_H(\cdot|\cdot)$ is similarly defined w.r.t. \mathcal{H} . Vansteelandt et al. (2008) obtain a closed form representation of the projection in \mathcal{H} of any function $D \in \mathcal{H}$ onto $(\mathcal{C}_0 \cup \mathcal{C}_1 \cup \mathcal{C}_2)^{\perp}$ as

$$J(D) - \frac{E\{D\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}|\mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}^{2}|\mathbf{C}\}}\tilde{S} - J\left(\frac{E\{D\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}\right)$$

where we define the $J(\cdot)$ operator on function D^* as

$$J(D^*) = D^* - \frac{E\{D^*\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{C}\}}$$

and

$$\tilde{S} = S - P_{\sigma}(\mathbf{Z}, \mathbf{C}).$$

Applying this result, we obtain the efficient score as

$$\begin{split} & \left[J(\mu(\mathbf{Z}, S, \mathbf{C})) - \frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}|\mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}^{2}|\mathbf{C}\}}\tilde{S} - J\left(\frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}\right) \right] \\ & \times \sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\epsilon^{*} \\ & = \left[\mu(\mathbf{Z}, S, \mathbf{C}) - \frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}} - \frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}|\mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}\tilde{S} \right] \\ & \times \sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\epsilon^{*} \end{split}$$

where we use that

$$E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{C}\}^{-1}E\left[\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}\Big|\mathbf{C}\right]$$
$$=E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{C}\}^{-1}E\left[E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}|\mathbf{C}\right]$$
$$=E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{C}\}^{-1}E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{C}\}.$$

To further simply the previous expression for the efficient score, note firstly that

$$P_{\sigma}(\mathbf{Z}, \mathbf{C}) = \frac{f(S = 1 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 1, \mathbf{C})}{f(S = 1 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 1, \mathbf{C}) + f(S = 0 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})}$$
$$= \frac{\frac{f(S = 1 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 1, \mathbf{C})}{f(S = 0 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})}}{\frac{f(S = 1 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})}{f(S = 0 | \mathbf{Z}, \mathbf{C}) \sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})} + 1}$$

and $1 - P_{\sigma}(\mathbf{Z}, \mathbf{C}) = E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\}^{-1}$. Secondly,

$$\frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}} = \frac{\mu(\mathbf{Z}, 1, \mathbf{C})\frac{f(S=1|\mathbf{Z}, \mathbf{C})}{f(S=0|\mathbf{Z}, \mathbf{C})}\frac{\sigma^{-2}(\mathbf{Z}, 1, \mathbf{C})}{\sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})} + \mu(\mathbf{Z}, 0, \mathbf{C})}{\frac{f(S=1|\mathbf{Z}, \mathbf{C})}{f(S=0|\mathbf{Z}, \mathbf{C})}\frac{\sigma^{-2}(\mathbf{Z}, 1, \mathbf{C})}{\sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})} + 1}$$
$$= \mu(\mathbf{Z}, 1, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C}) + \mu(\mathbf{Z}, 0, \mathbf{C})\{1 - P_{\sigma}(\mathbf{Z}, \mathbf{C})\}$$
$$= \delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C}) + \mu(\mathbf{Z}, 0, \mathbf{C})$$

and thus

$$\mu(\mathbf{Z}, S, \mathbf{C}) - \frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}} = \delta\mu(\mathbf{Z}, \mathbf{C})\tilde{S}$$

Thirdly,

$$\frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}|\mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}^{2}|\mathbf{C}\}} = \frac{E\left[\mu(\mathbf{Z}, 1, \mathbf{C})\frac{f(S=1|\mathbf{Z}, \mathbf{C})}{f(S=0|\mathbf{Z}, \mathbf{C})}\frac{\sigma^{-2}(\mathbf{Z}, 1, \mathbf{C})}{\sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})}\{1 - P_{\sigma}(\mathbf{Z}, \mathbf{C})\} - \mu(\mathbf{Z}, 0, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\right]}{E\left[\frac{f(S=1|\mathbf{Z}, \mathbf{C})}{f(S=0|\mathbf{Z}, \mathbf{C})}\frac{\sigma^{-2}(\mathbf{Z}, 1, \mathbf{C})}{\sigma^{-2}(\mathbf{Z}, 0, \mathbf{C})}\{1 - P_{\sigma}(\mathbf{Z}, \mathbf{C})\}^{2} + P_{\sigma}(\mathbf{Z}, \mathbf{C})^{2}|\mathbf{C}\right]} = \frac{E\{\delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}{E\{P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}$$

Putting all this together, we have

$$\begin{split} &\left[\mu(\mathbf{Z}, S, \mathbf{C}) - \frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C}) | \mathbf{Z}, \mathbf{C}\}} - \frac{E\{\mu(\mathbf{Z}, S, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}|\mathbf{C}\}}{E\{\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\tilde{S}^{2}|\mathbf{C}\}}\tilde{S}\right] \\ &\times \sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\epsilon^{*} \\ &= \left[\delta\mu(\mathbf{Z}, \mathbf{C}) - \frac{E\{\delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}{E\{P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}\right]\tilde{S}\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\epsilon^{*} \\ &= \left[\delta\mu(\mathbf{Z}, \mathbf{C}) - \frac{E\{\delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}{E\{P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}\right] \\ &\times P_{\sigma}(\mathbf{Z}, \mathbf{C})\{1 - P_{\sigma}(\mathbf{Z}, \mathbf{C})\}E\{\sigma^{2}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\}\frac{(-1)^{1-S}}{f(S|\mathbf{Z}, \mathbf{C})\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})}\sigma^{-2}(\mathbf{Z}, S, \mathbf{C})\epsilon^{*} \\ &= \left[\delta\mu(\mathbf{Z}, \mathbf{C}) - \frac{E\{\delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}{E\{P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\}}\right]P_{\sigma}(\mathbf{Z}, \mathbf{C})\frac{(-1)^{1-S}f(\mathbf{Z}|\mathbf{C})}{f(S, \mathbf{Z}|\mathbf{C})}\epsilon^{*}. \end{split}$$

This is of the form of equation (8), with admissible independence densities

$$f^{\ddagger}(\mathbf{Z}, S|\mathbf{C}) = \left(\frac{1}{2}\right)^{S} \left(\frac{1}{2}\right)^{1-S} f(\mathbf{Z}|\mathbf{C})$$

and optimal index

$$r_0^{opt}(\mathbf{Z}, S, \mathbf{C}) = \left\{ \delta\mu(\mathbf{Z}, \mathbf{C}) - \frac{E\left\{\delta\mu(\mathbf{Z}, \mathbf{C})P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\right\}}{E\left\{P_{\sigma}(\mathbf{Z}, \mathbf{C})|\mathbf{C}\right\}} \right\} 2(-1)^{1-S}P_{\sigma}(\mathbf{Z}, \mathbf{C}).$$

Note that

$$E^{\ddagger}\left\{r_{0}^{opt}(\mathbf{Z}, S, \mathbf{C})|\mathbf{Z}, \mathbf{C}\right\} = E^{\ddagger}\left\{r_{0}^{opt}(\mathbf{Z}, S, \mathbf{C})|S, \mathbf{C}\right\} = 0$$

confirming that the optimal index function is in the right subspace. Efficiency at the intersection submodel follows from general results in Robins and Rotnitzky (2001).

If **Z** is binary, then one can obtain the efficient score by obtaining the optimal choice $m_{opt}(\mathbf{C})$ of $m(\mathbf{C})$ in

$$\frac{m(\mathbf{C})(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\epsilon^*(\psi^{\dagger})$$

which can be done via a population least squares projection of the score $U_{\psi^{\dagger}}$ for ψ onto the above. Thus,

$$\begin{split} m_{opt}(\mathbf{C}) &= E\left[\left\{\frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\right\}^{2} \sigma^{2}(\mathbf{Z},S,\mathbf{C}) \middle| C\right]^{-1} E\left\{U_{\psi^{\dagger}} \frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})} \epsilon^{*} \middle| C\right\} \\ &= E\left[\left\{\frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\right\}^{2} \sigma^{2}(Z,S,\mathbf{C}) \middle| C\right]^{-1} E\left\{E(U_{\psi^{\dagger}} \epsilon^{*} | Z,S,\mathbf{C}) \frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})} \middle| C\right\} \\ &= E\left[\left\{\frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\right\}^{2} \sigma^{2}(Z,S,\mathbf{C}) \middle| C\right]^{-1} E\left\{\mu(\mathbf{Z},S,\mathbf{C}) \frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})} \middle| C\right\} \\ &= E\left[\left\{\frac{(-1)^{Z+S}}{f(Z,S|\mathbf{C})}\right\}^{2} \sigma^{2}(Z,S,\mathbf{C}) \middle| C\right]^{-1} \left\{\mu(Z=1,S=1,\mathbf{C}) - \mu(Z=1,S=0,\mathbf{C})\right\}. \end{split}$$

B.9 Proof of Theorem A.5

Proof. To obtain the efficient influence function for ψ , we must find the random variable G which satisfies:

$$\frac{\partial}{\partial r}\psi_r^*|_{r=0} = E\{GU(\mathbf{O};r)\}|_{r=0}$$

for $U(\mathbf{O}; r) = \partial \log\{f(\mathbf{O}; r)\}/\partial r$, where $f(\mathbf{O}; r)$ is a one-dimensional regular parametric submodel of \mathcal{M}_{np} . By the product rule,

$$\begin{split} \frac{\partial}{\partial r} \psi_r^*|_{r=0} &= \int \frac{\partial}{\partial r} \left(\frac{\delta_r^Y(\mathbf{c}) - t_r(1, \mathbf{c})}{\delta_r^A(\mathbf{c})} \right) \Big|_{r=0} dF(\mathbf{c}|A=1, S=1) \\ &+ \int \beta(\mathbf{c}) dF_r(\mathbf{c}|A=1, S=1) / \partial r|_{r=0} \\ &= (i) + (ii). \end{split}$$

If we first consider term (ii):

$$\begin{aligned} (ii) &= E \left\{ \beta(\mathbf{C}) U(\mathbf{C} | A = 1, S = 1) | A = 1, S = 1 \right\} \\ &= \frac{1}{f(A = 1, S = 1)} E \left\{ AS\beta(\mathbf{C}) U(\mathbf{C} | A, S) \right\} \\ &= \frac{1}{f(A = 1, S = 1)} E \left(AS\beta(\mathbf{C}) [E\{U(\mathbf{O}) | \mathbf{C}, A, S\} - E\{U(\mathbf{O}) | A, S\}] \right) \\ &= \frac{1}{f(A = 1, S = 1)} E \left[AS \left\{ \beta(\mathbf{C}) - \psi \right\} U(\mathbf{O}) \right]. \end{aligned}$$

Considering now term (i), then

$$(i) = \frac{1}{f(A=1,S=1)} E\left\{\frac{\partial}{\partial r} \frac{\delta_r^Y(\mathbf{C}) - t_r(1,\mathbf{C})}{\delta_r^A(\mathbf{C})}\Big|_{r=0} f(A=1,S=1|\mathbf{C})\right\}.$$

Following the steps in the proof of Theorem 5 in Wang and Tchetgen Tchetgen (2018),

$$\frac{\partial}{\partial r}E_r(Y|Z=z,S=s,\mathbf{C})|_{r=0} = E\left\{\frac{I(Z=z)I(S=s)}{f(Z,S|\mathbf{C})}\{Y-E(Y|Z,S,\mathbf{C})\}U(\mathbf{O})\Big|\mathbf{C}\right\}$$

and therefore

$$\frac{\partial}{\partial r} \{\delta_r^Y(\mathbf{C}) - t_r(1, \mathbf{C})\}|_{r=0} = E\left\{\frac{(2Z-1)(2S-1)}{f(Z, S|\mathbf{C})}\{Y - E(Y|Z, S, \mathbf{C})\}U(\mathbf{O})\Big|\mathbf{C}\right\}$$

and

$$\frac{\partial}{\partial r}\delta_r^A(\mathbf{C})|_{r=0} = E\left\{\frac{(2Z-1)S}{f(Z,S=1|\mathbf{C})}\{A - E(A|Z,S=1,\mathbf{C})\}U(\mathbf{O})\Big|\mathbf{C}\right\}$$

which gives us

$$\begin{aligned} (i) &= \frac{1}{f(A=1,S=1)} E\left[\frac{f(A=1,S=1|\mathbf{C})}{\delta^{A}(\mathbf{C})} \frac{(2Z-1)}{f(Z,S|\mathbf{C})} \\ &\times \{(2S-1)\{Y - E(Y|Z,S,\mathbf{C})\} - S\beta(\mathbf{C})\{A - f(A=1|Z,S=1,\mathbf{C})\}\}U(\mathbf{O})\right] \\ &= \frac{1}{f(A=1,S=1)} E\left\{\frac{f(A=1,S=1|\mathbf{C})}{\delta^{A}(\mathbf{C})} \frac{(2Z-1)}{f(Z,S|\mathbf{C})} \\ &\times \left(S[Y - E(Y|Z,S=1,\mathbf{C}) - \beta(\mathbf{C})\{A - f(A=1|Z,S=1,\mathbf{C})\}\right] \\ &- (1-S)\{Y - E(Y|Z,S=0,\mathbf{C})\}\right)U(\mathbf{O})\right\}. \end{aligned}$$

We furthermore have that

$$\begin{aligned} Y - E(Y|Z, S = 1, \mathbf{C}) &- \{A - E(A|Z, S = 1, \mathbf{C})\}\beta(\mathbf{C}) \\ &= Y - E(Y|Z = 0, S = 1, \mathbf{C}) - \delta^{Y}(\mathbf{C})Z - \beta(\mathbf{C})A + \beta(\mathbf{C})f(A = 1|Z = 0, S = 1, \mathbf{C}) + \beta(\mathbf{C})\delta^{A}(\mathbf{C})Z \\ &= Y - E(Y|Z = 0, S = 1, \mathbf{C}) - \beta(\mathbf{C})\delta^{A}(\mathbf{C})Z - t(1, \mathbf{C})Z \\ &- \beta(\mathbf{C})A + \beta(\mathbf{C})f(A = 1|Z = 0, S = 1, \mathbf{C}) + \beta(\mathbf{C})\delta^{A}(\mathbf{C})Z \\ &= Y - E(Y|Z = 0, S = 1, \mathbf{C}) - \beta(\mathbf{C})\{A - f(A = 1|Z = 0, S = 1, \mathbf{C})\} - t(1, \mathbf{C})Z \end{aligned}$$

such that

$$\begin{aligned} (i) &= \frac{1}{f(A=1,S=1)} E\left\{ \frac{f(A=1,S=1|\mathbf{C})}{\delta^{A}(\mathbf{C})} \frac{(2Z-1)}{f(Z,S|\mathbf{C})} \\ &\times \left(S[Y-E(Y|Z=0,S=1,\mathbf{C}) - \beta(\mathbf{C})\{A-f(A=1|Z=0,S=1,\mathbf{C})\} - t(1,\mathbf{C})Z] \\ &- (1-S)\{Y-t(1,\mathbf{C})Z - E(Y|Z=0,S=0,\mathbf{C})\} \right) U(\mathbf{O}) \right\} \\ &= \frac{1}{f(A=1,S=1)} E\left\{ \frac{f(A=1,S=1|\mathbf{C})}{\delta^{A}(\mathbf{C})} \frac{(2Z-1)(2S-1)}{f(Z,S|\mathbf{C})} \\ &\times [Y-E(Y|Z=0,S,\mathbf{C}) - \beta(\mathbf{C})\{A-f(A=1|Z=0,S=1,\mathbf{C})\}S - t(1,\mathbf{C})Z]U(\mathbf{O}) \right\}. \end{aligned}$$

The main result then follows by combining (i) and (ii).

C Simulation studies

C.1 Additional estimators

Two-stage least squares

Under NEM, a two-stage least squares estimator can be obtained by solving the equations

$$0 = \sum_{i=1}^{n} S_{i}m(\mathbf{Z}_{i}, \mathbf{C}_{i})\{Y_{i} - \beta(\mathbf{A}_{i}, \mathbf{C}_{i}; \psi^{\dagger})S_{i} - t(\mathbf{Z}_{i}, \mathbf{C}_{i}; \nu^{\dagger}) - b_{0}(\mathbf{C}_{i}; \theta_{1}^{\dagger}) - b_{1}(\mathbf{C}_{i}; \theta_{1}^{\dagger})S_{i}\}$$

for ψ^{\dagger} (Richardson and Tchetgen Tchetgen, 2021), where *m* is of the same dimension of ψ^{\dagger} . In practice, the unknown values ν^{\dagger} and θ^{\dagger} can be substitued by the estimates $\tilde{\nu}$ and $\hat{\theta}$ as described in Section A.7. Since this approach relies on a parametric model for the outcome, one can set $E(S|\mathbf{Z}, \mathbf{C})$ to zero in the equations for θ^{\dagger} ; this is what was done to obtain the estimator $\hat{\psi}_{TSLS}$ in the simulations.

G-estimation: two strategies

One can construct a g-estimator via solving the equations

$$0 = \sum_{i=1}^{n} S_i[m(\mathbf{Z}_i, \mathbf{C}_i) - E\{m(\mathbf{Z}_i, \mathbf{C}_i) | S_i = 1, \mathbf{C}_i; \tau^{\dagger}, \rho^{\dagger}\}$$
$$\times \{Y_i - \beta(\mathbf{A}_i, \mathbf{C}_i; \psi^{\dagger}) S_i - t(\mathbf{Z}_i, \mathbf{C}_i; \nu^{\dagger}) - b_0(\mathbf{C}_i; \theta_0^{\dagger}) - b_1(\mathbf{C}_i; \theta_0^{\dagger}) S_i\}$$

for ψ^{\dagger} . Richardson and Tchetgen Tchetgen (2021) note that the above equations are doubly robust, and yield an estimator that is unbiased under the union model $\mathcal{M}_{NEM} \cap$ $(\mathcal{M}_1 \cup \mathcal{M}_2)$ i.e. so long as either $f(\mathbf{Z}|S = 1, \mathbf{C})$ or $b_0(\mathbf{C})$ and $b_1(\mathbf{C})$ are correctly modelled. In order to obtain a doubly robust estimator, ν^{\dagger} must be estimated using a estimator consistent under the laws $\mathcal{M}_1 \cap \mathcal{M}_2$. In the simulations, ν^{\dagger} was estimated via the equations given in Section 3.2 for $\hat{\nu}$, with $b_0(\mathbf{C})$ fixed at zero; similarly, in the *g*-estimating equations used to estimate ψ as $\hat{\psi}_{g-Z}$, $b_0(\mathbf{C})$ and $b_1(\mathbf{C})$ were fixed at zero.

An alternative doubly g-estimator can be obtained as $\tilde{\psi}$ based on the equations in Section A.7, step 4; the resulting estimator is then unbiased under the union model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_3)$. In order to construct the estimator $\hat{\psi}_{g-S}$ in the simulations, we set $t(\mathbf{Z}, \mathbf{C})$ and $b_0(\mathbf{C})$ at zero.

Inverse probability weighted estimation

An inverse probability weighted (IPW) estimator can be obtained via solving the estimating equations:

$$0 = \sum_{i=1}^{n} \phi(\mathbf{Z}_{i}, S_{i}, \mathbf{C}_{i}; \tau^{\dagger}, \alpha^{\dagger}, \rho^{\dagger}) \{Y_{i} - \beta(\mathbf{A}_{i}, \mathbf{C}_{i}; \psi^{\dagger})S_{i}\}$$

for ψ^{\dagger} . One can show along the lines of the proof of Theorem 3.2 that the resulting estimator is unbiased under the model $\mathcal{M}_{NEM} \cap \mathcal{M}_4$. In the simulations, we estimated

 τ^{\dagger} , α^{\dagger} and ρ^{\dagger} as proposed in Section 3.2, in order to construct the estimator $\hat{\psi}_{IPW}$

C.2 Simulation set-up and results

We conducted a series of simulation studies to first evaluate the robustness properties of the proposed estimators from Section 3.2. Specifically, we generated covariates C_1 and C_2 from a Bernoulli distribution with expectation 0.5 and a standard normal distribution respectively; let $\mathbf{C} = (C_1, C_2)$. An unmeasured confounder U was also a random binary variable mean with expectation 0.5. Then the sample selection probability was f(S = $1|\mathbf{C}) = expit(-0.5 + C_1 + 0.6C_2 + 0.5C_1C_2)$, and Z was generated from a Bernoulli distribution where $f(Z = 1|\mathbf{C}) = expit(0.25C_1 - 0.25C_2 + 0.5C_1C_2)$. Generating S in this manner led to around 60% of individuals in a simulated data set being members of the target population (S=1). The exposure was simulated from a Bernoulli distribution with $f(A = 1|Z, S = 1, \mathbf{C}, U) = expit(1 - 1.5Z - 0.75C_1 - 0.3C_2 - 0.5C_1C_2 + U)$ for individuals in the population S = 1 and was fixed at zero for all others. Finally, we generated the outcome from the distribution

$$\mathcal{N}(1+U+0.5C_1+0.5C_2-0.5C_1C_2+Z(1-0.4C_1-0.4C_2+0.5C_1C_2) + S(A+0.5C_1+0.5C_2+0.5C_1C_2), 1).$$

This data generating mechanism is compatible with Assumptions 1-5, but not with conditional exchangeability if one does not have access to U. Nor would it be compatible with the instrumental variable conditions, since both the exclusion restriction and unconfoundedness are violated.

In our simulations, we considered a suite of estimators of the conditional average treatment effect on the treated in the target population, discussed in the previous subsection. Nuisance parameters were estimated using maximum likelihood, and a sandwich estimator was obtained for each of the estimators given above. For comparison, we also considered a doubly robust g-estimator that is valid under a conditional exchangeability assumption (Robins, 1994), where a linear model was fitted for the outcome, and a logistic model for the exposure; both models were adjusted for Z, C_1 , C_2 and a C_1C_2 interaction term. Furthermore, we also implemented a standard two-stage least squares estimator under the assumption that Z is a valid instrument. For both stages we fit models that were linear in the instrument/exposure, C_1 , C_2 and a C_1C_2 interaction term.

We considered five initial experiments:

1. All nuisance models are correctly specified: the intersection model $\mathcal{M}_{NEM} \cap \mathcal{M}_1 \cap \mathcal{M}_2 \cap \mathcal{M}_3 \cap \mathcal{M}_4$ holds.

2.
$$f(Z|S=0, \mathbf{C}; \tau^{\dagger})$$
 and $f(S|Z=0, \mathbf{C}; \alpha^{\dagger})$ were misspecified: $\mathcal{M}_{NEM} \cap \mathcal{M}_1$ holds.

3.
$$f(S|Z = 0, \mathbf{C}; \alpha^{\dagger}), b_0(\mathbf{C}; \theta_0^{\dagger}) \text{ and } b_1(\mathbf{C}; \theta_1^{\dagger}), \text{ were misspecified: } \mathcal{M}_{NEM} \cap \mathcal{M}_2 \text{ holds.}$$

4.
$$f(Z|S=0, \mathbf{C}; \tau^{\dagger})$$
, $b_0(\mathbf{C}; \theta_0^{\dagger})$ and $t(Z, \mathbf{C}; \nu^{\dagger})$, were misspecified: $\mathcal{M}_{NEM} \cap \mathcal{M}_3$ holds.

5.
$$t(Z, \mathbf{C}; \nu^{\dagger}), b_0(\mathbf{C}; \theta_0^{\dagger})$$
 and $t(Z, \mathbf{C}; \nu^{\dagger})$, were misspecified: $\mathcal{M}_{NEM} \cap \mathcal{M}_4$ holds.

Misspecification was induced via omission of interaction terms. For each setting, we simulated 2,000 data sets, with a sample size of 5,000.

We also performed simulations to evaluate violations of the identification assumptions. In experiment 6, we changed the outcome generating mechanism to

$$\mathcal{N}(1+U+0.5C_1+0.5C_2-0.5C_1C_2+ZS(1-0.4C_1-0.4C_2+0.5C_1C_2) + S(A+0.5C_1+0.5C_2+0.5C_1C_2), 1).$$

such that Z has no association with Y in the reference population, but does has an association in the target population. In experiment 7, we considered settings where the

Table 2: Simulations evaluating impact of model misspecification. Experiment (Exp), empirical bias for the conditional effect in the treated (Bias), empirical standard error (SE), coverage probability (Cov).

| | $\hat{\psi}_{TSLS}$ | | | $\hat{\psi}_{g-Z}$ | | | $\hat{\psi}_{g-S}$ | | | $\hat{\psi}_{g-IPW}$ | | | $\hat{\psi}_{MR-eff}$ | | |
|----------------------|---------------------|------|------|--------------------|------|------|--------------------|------|------|----------------------|------|------|-----------------------|------|------|
| Exp | Bias | SE | Cov | Bias | SE | Cov | Bias | SE | Cov | Bias | SE | Cov | Bias | SE | Cov |
| 1 | 0.01 | 0.26 | 0.95 | -0.00 | 0.41 | 0.95 | 0.01 | 0.23 | 0.96 | 0.01 | 0.33 | 0.95 | 0.01 | 0.23 | 0.95 |
| 2 | -0.00 | 0.27 | 0.95 | 0.08 | 0.39 | 0.94 | 0.18 | 0.26 | 0.89 | -0.54 | 0.28 | 0.48 | -0.01 | 0.24 | 0.94 |
| 3 | -0.59 | 0.25 | 0.35 | -0.02 | 0.41 | 0.95 | -0.30 | 0.22 | 0.73 | -0.36 | 0.28 | 0.74 | -0.01 | 0.23 | 0.95 |
| 4 | -0.51 | 0.26 | 0.48 | -1.13 | 0.36 | 0.10 | 0.00 | 0.24 | 0.95 | -0.25 | 0.32 | 0.85 | -0.00 | 0.23 | 0.95 |
| 5 | -0.58 | 0.25 | 0.34 | -0.42 | 0.36 | 0.80 | -0.14 | 0.22 | 0.92 | 0.00 | 0.33 | 0.95 | -0.00 | 0.23 | 0.95 |

association between Z and A is weak; the exposure was now generated as $f(A = 1|Z, S = 1, \mathbf{C}, U) = expit(1 - 0.25Z - 0.75C_1 - 0.3C_2 - 0.5C_1C_2 + U)$ for those with S = 1. Since the aim was to isolate potential bias due to failure of the identification assumptions, all models in experiments 6 and 7 were correctly specified.

The results of the experiments 1-5 can be seen in Table 2. As a comparison, the benchmark doubly robust g-estimator has a bias in all experiments of 0.24, with coverage probability <0.01. Furthermore, the benchmark two-stage least squares estimator had a bias of -2.35 with coverage probability 0. We see that the bias and coverage properties of the estimators reflect the theory; the multiply robust estimator is the only approach that maintains good coverage properties across all experiments. The g-estimator $\hat{\psi}_{g-Z}$ exhibited wide confidence intervals across settings and sometimes large bias when the models were misspecified; improvements could potentially be made via modelling $b_0(\mathbf{C})$ and making the estimator doubly robust e.g. unbiased under model $\mathcal{M}_{NEM} \cap (\mathcal{M}_1 \cup \mathcal{M}_2)$. The efficient multiply robust estimator outperformed the two-stage least squares estimator both in terms of bias in the presence of misspecification, but also precision when models were correct. The latter aspect is perhaps not totally surprising, given that two-stage least squares estimators are not necessarily efficient even when the conditional outcome mean is correctly specified (Vansteelandt and Didelez, 2018). Although we have only considered two covariates, we expect our estimators to scale with covariate dimension similarly to

other M-estimators.

Results for experiments 6-7 can be seen in in Table 3. The doubly robust g-estimator under no unmeasured confounding has a bias of 0.24 (coverage <0.01) in both experiments. The benchmark two-stage least squares estimator has a bias of -1.17 in experiment 6 and -16.8 in experiment 7 (coverage was zero in both experiments). We see that under violations of partial population exchangeability (experiment 6), estimators exhibit bias and all coverage guarantees are lost. Bias was nevertheless comparable to that of the benchmark two-stage least squares estimator (although this may be an artifact of the setting). When the association between A and Z was weakened, we see that estimators exhibit some finite sample bias, and potentially dramatic increases in variance (in particular, $\hat{\psi}_{g-IPW}$). Nevertheless the coverage of confidence intervals was conservative.

Table 3: Simulations evaluating impact of identification failure. Experiment (Exp), empirical bias for the conditional effect in the treated (Bias), empirical standard error (SE), coverage probability (Cov).

| | $\hat{\psi}_{TSLS}$ | | | | $\hat{\psi}_{g-Z}$ | | | $\hat{\psi}_{g-S}$ | | | $\hat{\psi}_{g-IPW}$ | | | $\hat{\psi}_{MR-eff}$ | | |
|-----|---------------------|------|------|-------|--------------------|------|-------|--------------------|------|-------|----------------------|------|-------|-----------------------|------|--|
| Exp | Bias | SE | Cov | Bias | SE | Cov | Bias | SE | Cov | Bias | SE | Cov | Bias | SE | Cov | |
| 6 | -1.18 | 0.27 | 0.00 | -1.19 | 0.40 | 0.14 | -1.27 | 0.26 | 0.00 | -1.32 | 0.31 | 0.01 | -1.23 | 0.24 | 0.00 | |
| 7 | 0.17 | 5.83 | 0.99 | 0.72 | 17.69 | 0.99 | 0.28 | 7.84 | 0.99 | -0.03 | 39.14 | 1.00 | 0.28 | 8.16 | 0.99 | |

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