Sensitivity analysis for transportability in multi-study, multi-outcome settings

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Abstract

Existing works in data fusion have covered identifications of causal estimands when integrating data from heterogeneous sources. These results often require additional assumptions to make valid estimation and inference. However, there is little literature on transporting and generalizing causal effects in multiple-outcome setting, where the primary outcome is systematically missing on the study level but for which other outcome variables may serve as proxies. We review an identification result developed in ongoing unpublished work that utilizes information from these proxies to obtain more efficient estimators and the identification assumption. We then introduce methods for assessing the sensitivity of this approach to the identification assumption.

1 Introduction

Existing methodologies in generalizability and transportability involve directly extrapolcating the estimated average treatment effect (ATE) from the studies where the outcomes are observed to other studies with missing outcomes or to the larger population [4, 5, 10, 11, 12, 13, 14, 15]. When considering multiple studies, it is often the case that they will observe different outcomes at follow up. However, existing methods do not take advantage of these other potentially correlated and informative outcome variables measured at follow-up, which could potentially be leveraged to achieve large efficiency gains. Existing methods typically rely on the assumption of homogeneous conditional potential outcome means for plausible transportation of estimation from one population to another. Sensitivity analysis strategies have been proposed to study the extent to which the violation of these assumptions will affect the estimations and inferences drawn [6, 7].

In ongoing unpublished work, we developed a new identification strategy to efficiently estimate the ATE from integrated data across multi-outcome studies, with inconsistent availability of the primary outcome of interest at the study level. The proposed methodology takes advantage of the availability of follow-up measurements of potential correlates of the main outcome to yield more precise estimate of the parameter of interest. The main goal for this paper is to discuss the resulting bias in the estimator when the key assumption for transportability is not met, and present sensitivity analyses to the violation of this assumption.

2 Data integration for studies with primary outcome missing systematically

2.1 Study and data setting

Suppose there are S studies that are ordered such that in the first s^* studies, we observe the set of variables (Y, A, J_s, W), while in the remaining $S - s^*$ studies, only the subset (A, J_s, W) was measured. In other words, Y was systematically missing in the latter. In this setting, we let A be the treatment indicator, W be a set of covariates that are commonly observed across studies, Y be the primary outcome variable, and J_s be a subset of potential outcome proxies $\{T_1, \ldots, T_k\}$ measured at follow-up in study s that are potential correlates of Y. Unlike the standard setup in other works concerning effect transportability which usually only involves (Y, A, W) [13], we introduced the use of T_s, where $T_s \subset J_s$ is some user-specified subset of J_s for each study s. T_s could be chosen based on availability and subject matter knowledge and must be chosen such that they are observed in at least one of the studies $\{1, 2, \ldots, s^*\}$.

Studies can be randomized or observational (A can be independent of or dependent on baseline covariates in an unknown fashion). Then the study-specific average treatment effect and conditional average treatment effect can be written as:

$$ATE(s) = E(Y_1 - Y_0 \mid S = s)$$
$$CATE(w, a) = E(Y_1 - Y_0 \mid W = w, S = s).$$

Accordingly, we can define the generalized average treatment effect and conditional average treatment effect as:

$$ATE(s) = \sum_{s=1}^{S} ATE(s)$$
$$CATE(w, a) = E(Y_1 - Y_0 \mid S = s)$$

where the weights can be user-specified. For instance, one can choose $\pi_s = P(S = s)$, or the marginal probability of being in each study such that $\sum_{\pi_s} = 1$.

Since Y is not measured in $s \in \{s^* + 1, \ldots, S\}$, we cannot directly estimate the ATE and CATE using data from these studies alone. Our purpose is to transport the ATE from the first s^* studies where Y is observed, to the remaining $S - s^*$ studies while also leveraging the information from the outcome proxy set T_s to improve efficiency. For ease of notation, let the first s^* studies be described by the set σ_S. In this setting, we show in ongoing work that the ATE can be nonparametrically identified as:

$$\begin{aligned}\Psi^{ATE} = &\sum_{s=1}^{s^*} \pi_s E\{E(Y \mid W, A = 1, S = s) - E(Y \mid W, A = 0, S = s) \mid S = s\} \\ &+ \sum_{s=s^*+1}^{S} \pi_s E[E\{E(Y \mid T_s, W, A = 1, S \in \sigma_s) \mid W, A = 1, S = s\} \\ &\qquad - E\{E(Y \mid T_s, W, A = 0, S \in \sigma_s) \mid W, A = 0, S = s\} \mid S = s]\end{aligned} \tag{1}$$

Here, we introduced a modification to how transportability has traditionally been done by incorporating information from a set of outcomes measured at follow-up that are correlated with the main outcome of interest.

2.2 Assumptions for Identification of the ATE

This derivation ATE can be nonparametrically identified given the assumptions that are standard for identification for ATE when outcomes are all observed:

(C1) Positivity $P(A = 1 \mid W = w) > 0$.

(C2) Consistency: $Y = AY_1 + (1 - A)Y_0$.

(C3) Conditional exchangeability within study: $E[Y^a \mid T_s.W, S, A] = E[Y^a \mid T_s, W, S]$.

The validity of our estimator relies on a fourth assumption that allows for the transportation of the effect across studies:

$$E(Y \mid T_s, W, A = a, S = s) = E(Y \mid T_s, W, A = a, S \in \sigma_s) \quad \text{for all } s. \tag{C4}$$

We can also introduce a fifth assumption that is not necessary for identification, but allows for borrowing of information across studies which can help with efficiency:

$$T_s \perp S \mid W, A \tag{C5}$$

This implies the distribution of f T_s conditional on treatment assignment and baseline covariates is the same across studies. Under this additional assumption, the identification result simplifies to:

$$\begin{aligned} ATE = \sum_{s=1}^{s} \pi_s E[E\{E(Y \mid T_s, W, A = 1, S \in \sigma_s) \mid W, A = 1\} \\ - E\{E(Y \mid T_s, W, A = 0, S \in \sigma_s) \mid W, A = 0\} \mid S = s]. \end{aligned}$$

In ongoing work, we describe a simple substitution estimator that involves replacing each expectation with a regression-based estimate and the outer expectation with an empirical mean. For the outcome-regression based approach, on top of the standard first three assumptions, the mean outcome exchangeability across studies assumption (exchangeability over S) needs to hold [6, 13]. Our two assumptions (C4) and (C5) when combined imply this other assumption. For this paper, we will only consider sensitivity analysis for the violation of Assumption (C4). When Assumption (C5) is violated, the ATE estimator will remain consistent.

3 Characterizing the bias resulting from violation of the identification assumption

The validity of Ψ^{ATE} is dependent on the key assumption (C4). This assumption requires no heterogeneity in the conditional outcome means given treatment, covariates, and outcomes proxies between studies with and without missing outcome data. This allows for transportation of the conditional outcome means, and correspondingly, the ATE and CATE, estimable from one study to others.

In practice, this could be a strong assumption to make while also untestable using observed data. For instance, in previous unpublished work, we estimated the average treatment effect of cognitive remediation therapy (CR) on Social Beheavioral Scale (SBS) score, a measure for social functioning, using harmonized data from three trials in the NIMH Database of Cognitive Training and Remediation Studies (DoCTRS) database. However, the degree of effectiveness of CR, especially on functional and occupational outcomes, has not been shown to be consistent [1, 2, 16]. Assuming the conditional means to be homogeneous across studies, especially when clinical trials tend to be unrepresentative samples of the population and might be dissimilar in patients' baseline characteristics as well as outcomes. When this assumption is violated, the substitution estimators described in the previous section will be biased. Therefore, we examine two strategies for sensitivity analysis in order to examine the robustness of estimates under varying degrees of assumption violation.

When there is a violation of assumption (C4), the conditional average treatment effects cannot be transported across the two types of studies without incurring bias. To quantify the degree of violation, let the bias functions be defined as:

$$\begin{aligned} u(A = 1, T_s, W) &= E(Y \mid T_s, W, A = 1, S = s) - E(Y \mid T_s, W, A = 1, S \in \sigma_s), \\ u(A = 0, T_s, W) &= E(Y \mid T_s, W, A = 0, S = s) - E(Y \mid T_s, W, A = 0, S \in \sigma_s) \end{aligned} \tag{2}$$

Then, the identification result in (1) when assumption (C4) is violated becomes:

$$\begin{aligned}\text{ATE} = \sum_{s=1}^{s^*} \pi_S E\{E(Y \mid W, A=1, S=s) - E(Y \mid W, A=0, S=s) \mid S=s) \\ + \sum_{s=s^*+1}^{\text{S}} \pi_s E\left[E\left\{E\left(Y \mid T_s, W, A=1, S \in \sigma_s\right) \mid W, A=1, S=s\right)\right\} \\ - E\left\{E\left(Y \mid T_S, W, A=0, S \in \sigma_s\right) \mid W, A=0, S=s\right)\right\} \mid S=s] \\ + \sum_{s=s^*+1}^{\text{S}} \pi_s E[E\left\{u\left(A=1, T_s, W\right) \mid W, A=1, S=s\right\} - E\left\{u\left(A=0, T_S, W\right) \mid W, A=0, S=s\right\} \mid S=s]\end{aligned}$$

Then, the study-specific bias for study s is:

$$\begin{aligned}&E\left[E\left\{u\left(A=1, T_s, W\right) \mid W, A=1, S=s\right\} - E\left\{u\left(A=0, T_s, W\right) \mid W, A=0, S=s\right\} \mid S=s\right] \\ =&E[\delta^*(W) | S=s]\end{aligned} \tag{3}$$

By rearranging terms, $\delta^*(W)$ can be alternatively written as:

$$\begin{aligned}&E\left[E\left(Y \mid T_S, W, A=1, S=s\right) - E\left(Y \mid T_S, W, A=1, s \in \sigma_S\right) \mid W, A=1, S=s\right] \\ &\quad - E\left[E\left(Y \mid T_S, W, A=0, S=s\right) - E\left(Y \mid T_S, W, A=0, s \in \sigma_S\right) \mid W, A=0, S=s\right] \\ &= E(Y \mid W, A=1, S=s) - E(Y \mid W, A=0, S=s) \\ &\quad - \{E\left[E\left(Y \mid T_S, W, A=1, s \in \sigma_S\right) \mid W, A=1, S=s\right] \\ &\quad\quad - E\left[E\left(Y \mid T_S, W, A=0, s \in \sigma_S\right) \mid W, A=0, S=s\right]\}\end{aligned} \tag{4}$$

4 Comparison with bias functions in settings without incorporation of follow-up surrogate outcomes

Recent work developing sensitivity analysis for transportability [6] considers a similar setting of two types of studies with and without missing outcomes. In the base case, there are two studies considered (missingness of the outcome variable denoted by a binary indicator S), but this can be generalized to multiple studies. The imputation model does not utilize information from other outcome proxies T_s measured at follow-up.

In the setting where the model used to impute conditional potential outcomes does not utilize information from T_s, existing sensitivity method [6] defines:

$$u(A=a, W) = E[Y \mid A=a, W, S \in \sigma_s] - E[Y \mid A=a, W, = s]$$

The difference between these bias functions can then be obtained as:

$$\begin{aligned}\delta(W) &= u(A=1, W) - u(A=0, W) \\ &= E[Y^1 - Y^0 \mid W, S \in \sigma_s] - E[Y^1 - Y^0 \mid W, S=s]\end{aligned}$$

This expression can be qualitatively expressed as the difference in the conditional average treatment effects between the two studies. This qualitative interpretation can aid in conceptualizing and thinking about more appropriate values and range for sensitivity parameters when examining robustness of the results. More specifically, assuming higher levels of the outcome are preferred, if we believe the participants in studies with missing outcomes benefit less from treatment, then true δ can be assumed to be positive and vice versa [6]. Since our bias functions are conditional on the set of proxy outcomes, the term $\delta^*(W)$ in (4) unfortunately cannot be reduced further to a more interpretable statistical entity. It turns out that when we take T_s to be an empty set, the bias function $\delta^*(W)$ reduces to the same expression.

5 Accounting for violation of the key assumption though sensitivity analyses

We consider two scenarios in which we assume the bias terms $u(A=1,T_s,W)$ and $u(A=0,T_s,W)$ to be 1) constants and 2) bounded functions of the outcome proxies and/or baseline covariates. The first scenario involves making a stronger assumption about the bias terms. On the other hand, the second scenario requires weaker assumptions but allow them to be non-constant.

5.1 Bias functions assumed to be some fixed values

Although it might be more reasonable to assume that the bias functions are dependent on some baseline covariates, for ease of implementation of sensitivity analysis, one can also suppose they are constant. When $u(A=1,T_s,W)$ and $u(A=0,T_s,W)$ are independent of the baseline covariates W and the surrogate outcome set T_s, the conditional expectations of the bias functions, and in turn, the term $\delta^*(W)$ in (3), reduce to:

$$\delta = u_1 - u_0, \text{ where } \delta, u_1, \text{ and } u_0 \in \mathbb{R} \tag{5}$$

The sensitivity analysis involves correcting for the abovementioned bias term by adding it back to the identification formula assuming no violation of the transportability assumption.

$$\begin{aligned} ATE =& \sum_{s=1}^{S} \pi_S E\left\{E\left(Y \mid W, A=1, S \in \sigma_S\right) - E\left(Y \mid W, A=0, S \in \sigma_S\right) \mid S=s\right\} \\ &+ \sum_{s=s^*+1}^{S} \pi_s E\left[E\left\{E\left(Y \mid T_s, W, A=1, S \in \sigma_s\right) \mid W, A=1, S=s\right\}\right. \\ &\left. - E\left\{E\left(Y \mid T_S, W, A=0, S \in \sigma_s\right) \mid W, A=0, S=s\right\} \mid S=s\right] + \sum_{s=s^*+1}^{S} \pi_s \left(u_1 - u_0\right) \\ =& \Psi^{ATE} + \sum_{s=s^*+1}^{\mathrm{S}} \pi_s \left(u_1 - u_0\right) \end{aligned} \tag{6}$$

where u_1 and u_0 are scalars.

In practice, the true bias term would be unknown. Thus, one strategy is to propose a grid of sensitivity parameters that covering the potential range of values in which the true bias term might fall. This grid of sensitivity parameters can be specified using subject-matter knowledge. We can then adjust for the bias term in the estimation step by adding back the different sensitivity parameters to the estimated ATE using our proposed method. This also allows for observation of the behavior of the estimated ATE as we vary the sensitivity parameters.

5.2 Bounded covariate-dependent bias functions

One might also believe that the bias term is not constant at all levels of the baseline covariates and/or the outcome proxies. When the assumption of fixed-value bias terms is considered too strong, but the functional forms for bias terms cannot be confidently determined from existing knowledge of the data mechanism (as will typically be the case), one can still recover some information about the true ATE through partial identification without having to correctly specify the bias terms. If we assume the bias terms to be some bounded functions, we can compute a bound around the (naïve) ATE estimate that contains the true ATE. This provides information on how far away the true ATE can be from the estimate obtained constrained by the bounds of the bias term.

Identifying the bounds for the bias term can be expressed as maximizing and minimizing the objective function:

$$E[E[u(A=1,T_s,W) \mid W, A=1, S=s] - E[u(A=0,T_s,W) \mid W, A=0, S=s] \mid S=s]$$

subject to the following constraints:

$$|u(A=1,T_s=t_s,W=w)| \leq \gamma_1$$
$$|u(A=0,T_s=t_s,W=w)| \leq \gamma_0$$

for all t_s and w

which implies $|E[u(A=1,T_s,W) \mid W, A=1, S=s]| \leq \gamma_1$ and $|E[u(A=0,T_s,W) \mid W, A=0, S=s]| \leq \gamma_0$ where $\gamma_1, \gamma_1 \in \mathbb{R}^+$.

Then we have: $-(\gamma_1+\gamma_0) \leq u(A=1,T_s,W) - u(A=0,T_s,W) \leq \gamma_1+\gamma_0$, or $-2\max(\gamma_1,\gamma_0) \leq u(A=1,T_s,W) - u(A=0,T_s,W) \leq 2\max(\gamma_1,\gamma_0)$.

By equation (6) even though we do not know the form of the bias functions $u(A=1,T_s,W)$ and $u(A=0,T_s,W)$, we can partially recover the true ATE using the bounds around the naive estimate:

$$\Psi^{ATE} - 2\max(\gamma_1,\gamma_0) \leq ATE \leq \Psi^{ATE} + 2\max(\gamma_1,\gamma_0)$$
$$\Psi^{ATE} - 2\gamma \leq ATE \leq \Psi^{ATE} + 2\gamma \tag{7}$$

If the bias functions are in fact bounded by some value equal or smaller than our specified values for the sensitivity bounds, the true ATE would fall between $[ATE(1) - 2\gamma, \Psi^{ATE} + 2\gamma]$. Then, the

true ATE is partially identified without assumptions about the functional form of $u(A = 1, T_s, W)$ and $u(A = 0, T_s, W)$. Regarding inferences, since we can compute the bound on true ATE during each simulation, a confidence region for this bound can also be obtained by bootstrapping the end points.

6 Simulations

6.1 Data generating mechanism

Without loss of generality, we consider the setting of two studies, with S = 1 indicating the study where the primary outcome is available. We generate random sample draws with sample size n = 100 for both studies. The data generating mechanism is as follows. W, T_0 come from independent standard normal distributions, and T_1 comes from a normal distribution with mean and variance of 1. Then

$$\begin{aligned} T &= I(A = 1) \times T_1 + I(A = 0) \times T_0 \\ Y^0 &= -4T_0 + W + \epsilon_0 \\ Y^1 &= 4T_1 + W + \epsilon_1 \\ Y &= I(A = 1) \times Y_1 + I(A = 0) \times Y_0 \end{aligned}$$

where $\epsilon_1, \epsilon_0 \sim N(0, 1)$.

Via these specifications, T fully mediates the relationship between A and Y (direct effect from A to Y is constrained to be 0). As a result, the true ATE $= Y^1 - Y^0 = 4$. This is also a more basic setting in which the vector T is observed in all studies.

Due to the nature of the DoCTRS database, which is comprised of randomized clinical trials, in our base setting, we specified the marginal probability P(A = 1) = 0.5, representing random treatment assignment. This treatment assignment satisfies the positivity and exchangeability assumption. In the observational data setting, the probability of receiving treatment is generated as:

$$P(A = 1 \mid p_s) = \text{expit}\left(\log \frac{p_s}{1 - p_s} + \epsilon\right) \quad \text{where } \epsilon \sim N(0, 1)$$

where p_s is user-specified where it indicates the probability of receiving treatment. Specifically, when $p_s = 0.5$, treatment assignment is random (RCT); otherwise, the probability of receiving treatment is a function of baseline covariates (as in observational studies).

We then introduced bias directly into counterfactual outcomes via their definitions in (2). As we only have two studies in the base case, we can let S be an indicator for missing (S = 0) and observed (S = 1) outcomes.

Specifically, to incorporate the difference in conditional outcome means between the two types of studies, in studies with missing outcome, we added the bias terms $E[u(A = 0, T_s, W) \mid A = 0, S = 0]$

to the counterfactual outcome Y_0 (under no treatment) and added $E[u(A=1,T_s,W) \mid A=1,S=0]$ to the counterfactual outcome Y1 (under treatment):

$$\begin{aligned} Y^0_{S=1} &= Y^0_{S=0} + E\left[u\left(A=0,T_s,W\right) \mid W,A=0,S=s\right] \\ Y^1_{S=1} &= Y^1_{S=0} + E\left[u\left(A=1,T_s,W\right) \mid W,A=1,S=s\right] \end{aligned} \tag{8}$$

Similar to the data generating step, we preserved the observed counterfactual outcome from the corresponding treatment assignment, which satisfies the consistency assumption.

Assuming the true bias terms are constants, we simply replaced the bias terms above with constants and by (5), we have:

$$\begin{aligned} Y^0_{S=1} &= Y^0_{S=0} + u_0 \\ Y^1_{S=1} &= Y^1_{S=0} + u_0 + \delta \end{aligned} \tag{9}$$

where $u_0, \delta \in \mathbb{R}$.

Then the bias reduces to a single parameter δ, since it is no longer a function of u_0 when computing the ATE:

$$Y^1_{S=1} - Y^0_{S=1} = Y^1_{S=0} - Y^0_{S=0} + \delta \tag{10}$$

In the case where the bias term is a function of baseline covariates and surrogate outcome, we had the following specification for the true bias:

$$\begin{aligned} u_0 &= b_0 \times \sin\left(T_s + W\right) \\ u1 &= b_1 \times \tfrac{\exp(T_s+W)}{1+\exp(T_s+W)} \end{aligned}$$

where $b_0 \in \{2,3,4\}$ and $b_1 \in \{1,2,3\}$.

6.2 Adjusting for sensitivity parameter in estimation step

Scenario 1. When the bias terms are assumed to be constants, a natural approach would be to specify a two-dimensional grid of sensitivity parameters for both scalars u_0 and u_1. However, by (9), it is equivalent to specifying u_0 (or u_1) and δ. In fact, since the u_0 (or u_1) as constant terms cancel out during adjustment, it is sufficient to specify one sensitivity parameter δ (10).

To implement sensitivity analysis, we follow the steps:

1. Specify a grid of sensitivity parameters δ. The grid should be reasonably wide to contain true δ.
2. Estimate the transported ATE using the identification result in (1)
3. Sequentially add the values in the sensitivity parameter grid to the estimated ATE, using the result in (6) to obtain the bias-corrected ATE estimates.

We then plotted the bias-corrected estimates under different sensitivity parameters against the true ATE. Additionally, we bootstrapped the bias-corrected estimates to obtain the 95% confidence intervals and explore coverage across different values of u_0 and δ.

Scenario 2. When we want to make minimal assumptions about the functional form of the bias, we can still perform sensitivity analysis on the true ATE using the following steps:

1. Specify a grid of sensitivity parameters called γ that potentially include the upper and lower bounds of the true bias functions
2. Computed the "naïve" ATE estimate using the identification result in (1)
3. Construct the upper and lower bound around the estimated ATE using (7) where γ is replaced with the sensitivity parameters.

We also plot the naïve ATE estimates and the bounds around these estimates at each value of the sensitivity parameters. In practice, the bias functions are of course unknown and cannot be estimated from observed data. Therefore, when specifying the grid of sensitivity parameters, the analyst needs to employ subject matter knowledge about the data generating mechanism to select values of δ and γ.

We then explore the behavior of the bias-corrected estimators via simulations. In the first case, we focused on the general unbiasedness of the bias-corrected point estimate for both the overall ATE and ATE among studies with missing outcomes, as well as the 95% CI coverage across degrees of assumption violation (i.e., across values of true u_0 and δ). In the second case, we looked for correct partial identification of the true ATE (i.e., the true parameter lies inside the bound).

6.3 Simulation Results

6.3.1 Bias terms as constants

We examine the estimates produced by our method under the different degrees of violation of assumption (C4), before and after taking into account the specified sensitivity parameter. Figure 1 shows the estimates (95% CI) for the true overall ATE using our method under varying magnitudes and directions of the bias terms from one single simulation. In the presence of non-zero bias, it can be observed that when the value of the sensitivity parameter δ is specified such that it is equal to true δ, the ATE estimate after bias adjustment is generally closer to the true ATE after compared to before. In addition, the corresponding 95% CIs are expected to cover the true ATE 95% of the times. Although coverage probability can be examined more in a more robust fashion using bootstrapped confidence intervals across all simulations, in Figures 1,2, and 7-10, the 95% CIs almost always cover the true ATE at the value of the sensitivity parameter that reflects the degree of assumption violation, which is in line with our expectations.

Figure 2 shows similar results for the ATE estimates among studies with missing outcomes (before and after bias adjustment) from the same simulated data. Compared to the results in Figure 1,

after adjustment using the correct sensitivity parameters, the 95% CIs contain the true ATE more frequently than the CIs of the unadjusted estimates in the study with missing primary outcome. Figure 2 also shows an example where inference is sensitive to the violation of our assumption at a magnitude of δ about -2 ($u_0 = -3$, bottom left panel), beyond which point the 95% CI changes from not containing to zero to containing zero (or vice versa).

When we increased the sample size (n=200 and n=500), we saw general reductions in the errors of these single estimates (Figures 7 and 9). In most cases, even when the there is error in the adjusted estimates, the 95% CI bootstrap confidence intervals provide good coverage (Figures 1, 7, 9). The reduction in error and improved coverage are more pronounced when estimating the study-specific effect in the study with missing outcomes than in the overall ATE combining the two studies (Figures 8 and 10).

We also ran 1000 simulations under the same data generating mechanism and obtained the unadjusted and sensitivity-parameter-adjusted estimates for each simulation. We then showed the mean and 2.5th and 97.5th quantiles of these estimates under each combination of the true bias values. We can see that when averaged across 1000 simulations, the adjusted estimates closely approximate the true ATE (Figures 3 4) when the true value of δ is used for the sensitivity parameter. When approximate sensitivity parameters δ are used ($\delta \in \{-1, 1\}$ when true $\delta \in \{-2, 2\}$), the middle 95% values of adjusted estimates also cover the true ATE whereas those of unadjusted estimates do not (Figure 4).

Figure 5 compares the errors in the estimates and sensitivity of associated inferences between the outcome regression method [6, 13] and the proposed method across 1000 simulations. When averaged across simulations, both methods' estimates are closely approximate the true parameter. However, the estimates tend to be more precise when we utilize the information from the outcome proxy (as demonstrated through the narrower 2.5th-97.5th quantile range). The efficiency gains have implications for the sensitivity analysis, since resulting inferences are not as sensitive given the same magnitude in violation of the identification assumption (C4).

Assumption (C4) implies both u_0 and u_1 equal 0.As a result, the true δ also equals 0. This suggests transportation of the conditional potential outcome means, and in turn, the conditional average treatment effects, can be done without incurring bias (vertical middle panes, figure 3). We also observed that, when δ is 0, regardless of the values of u_0 (and u_1), there is also no bias (vertical middle panes, figure 3) in the unadjusted estimator. In both cases, no bias correction would be necessary, and incorporating a non-zero sensitivity parameter will actually introduce bias to the estimate. We also note that δ being 0 does not necessarily imply assumption (C4) is met, since the bias terms u_0 and u_1 could cancel exactly.

6.3.2 Bias terms as bounded functions

When the sensitivity parameter γ is greater or equal to $\max\{\gamma_0, \gamma_1\}$, the bounds always include the true ATE when the bias functions are bounded by γ_0 and γ_1 (Figure 6). Although this approach requires minimal assumptions about the bias functional form, it can also be conservative since 1) the true bias functions are unlikely to evaluate to the bounds across the domain of the functions, and 2) we use only one sensitivity parameter $\gamma = \max\{\gamma_0, \gamma_1\}$ rather than individually specifying γ_0

and γ_1 to compute the bound (7). For instance, the top bottom three panels of Figure 6 show that when the sensitivity parameter γ is equal to or greater than max(true γ_0, true γ_1), the bound on the estimate contains the true ATE but also crosses the null value 0, which might be more conservative than we would like. On the other hand, these bounds do not rely on an assumption of constant bias functions, which we may often have no reason to believe. Figure 6 also illustrates that for smaller sensitivity parameters γ, the bounds are narrower and more likely to be more informative (i.e., do not contain 0). Similarly, smaller true γ_0 and γ_1 relative to the true ATE are more likely to yield informative bounds for the parameter. Here, we demonstrated through simulations that sensitivity analysis with relaxed and more credible assumptions can still provide helpful information about the parameter of interest. However, when the bounds are too narrow or too wide, sensitivity analysis using bounded bias functions might not be accurate (i.e., not containing the true parameter) or useful (i.e., containing the null value when the truth is non-null), respectively.

7 Discussion

In this paper, we discussed a data integrative method that utilizes information from available proxies of the outcome of interest measured at follow-up for efficiency gains. We then presented two sensitivity analysis strategies specific to this approach for causal effect transportation when the identification assumption is violated. Our modification to the identification of the ATE in (1) allows for more efficient estimators given sufficiently strong outcome proxies. As a result, our bias functions also have similar, yet distinct interpretations than the bias functions of [6, 7].

When the bias terms are assumed to be constants, we can obtain different bias-adjusted point estimates based on our assigned values for the true bias terms. Additionally, via obtaining the 95% bootstrap confidence interval for the bias-adjusted estimates, we can examine the robustness of inferences made using our method under varying magnitudes of assumption violation. Specifically, beyond certain values of the sensitivity parameters, the 95% CI will cross the null value 0. These are the degrees of violation that can affect inferences (where the 95% CI suggest a change from significant results to non-significant results).

We also proposed sensitivity analysis using bounded bias functions as an alternative when one believes the assumption of a fixed-value bias term is too strong. This approach allows for inferences with minimal assumptions about the unobserved bias functions but can still provide useful information about the parameter of interest. Due to fewer assumptions being made, the results are more conservative and robust, hence more reasonable and credible. Specifically, although we are unable to obtain a point estimate, sensitivity analysis using bounded bias functions can still be informative in the sense of providing information about the general direction of the parameter of interest (beneficial or harmful). This method is generally more conservative if the bounds on the functions are large compared to the true bias functions (especially when true causal effect of interest is small), or if there is a large difference between the bounds of the bias functions.

Correct specification of the bias functions would allow for more precise and informative estimation of the true ATE. However, since they are generally unknown and non-estimable from observed data, sensitivity analysis will typically be the realistic course of action.

When conducting sensitivity analysis, the analyst can start off by specifying a wide grid of the sensitivity parameter and examining the behaviors of the point estimates and 95% CI (first approach) as well as bounds around the estimates (second approach). They can then search for the "critical" sensitivity parameters that still suggest rejection of the null hypothesis, i.e., the 95% CI (in the first case) and bounds around the estimate (in the second case) do not contain 0. It can be determined if greater bias is plausible by using background knowledge of the data generating mechanism or further hypothesizing about such mechanism. If there is little or no evidence that the true bias functions exceed these critical sensitivity parameters, one can be more comfortable in concluding that the observed effect and associated inferences are robust to violation of the transportability assumption [9, 3].

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A Figures

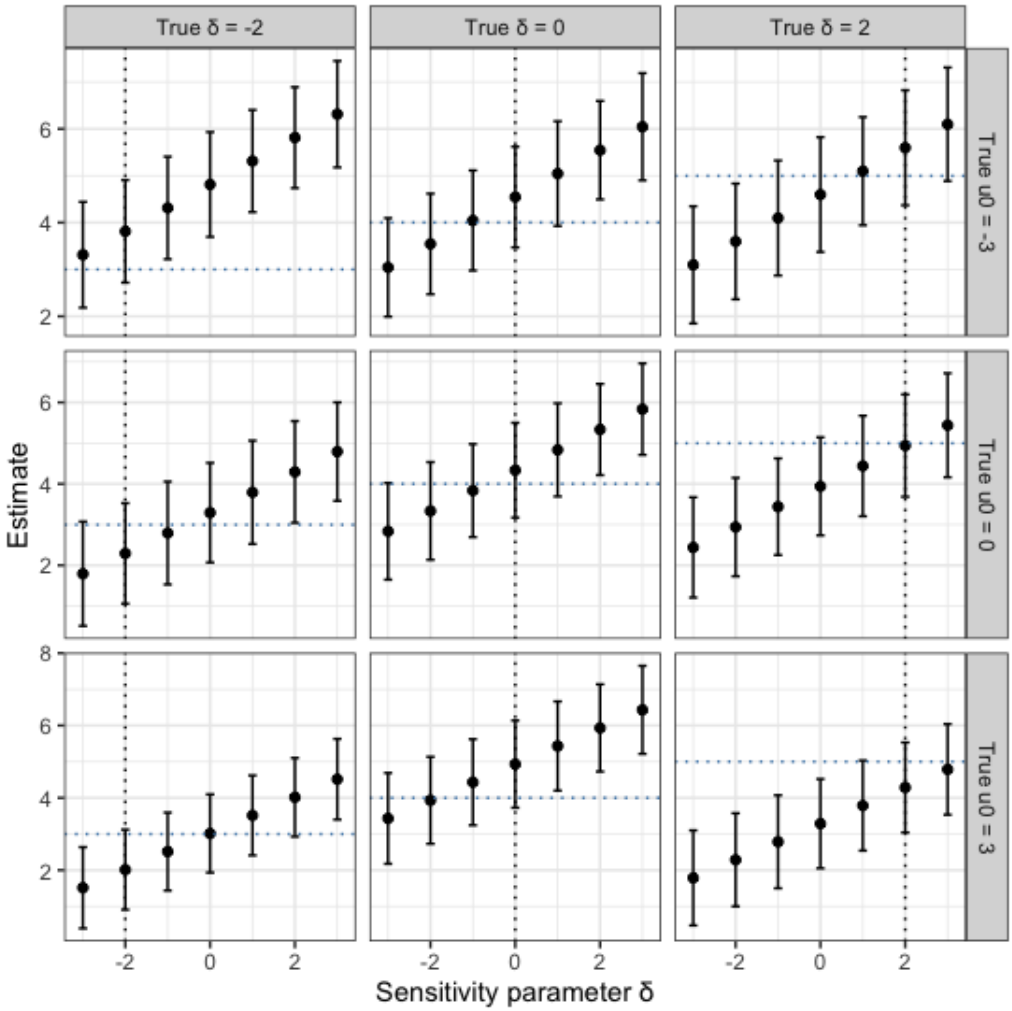

Figure 1: Sensitivity-parameter-adjusted ATE estimate shown against the true overall ATE across values of the true bias and sensitivity parameter; n=100 for each study, 95% CI constructed from 1000 bootstrap samples. Horizontal dotted line shows the true ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

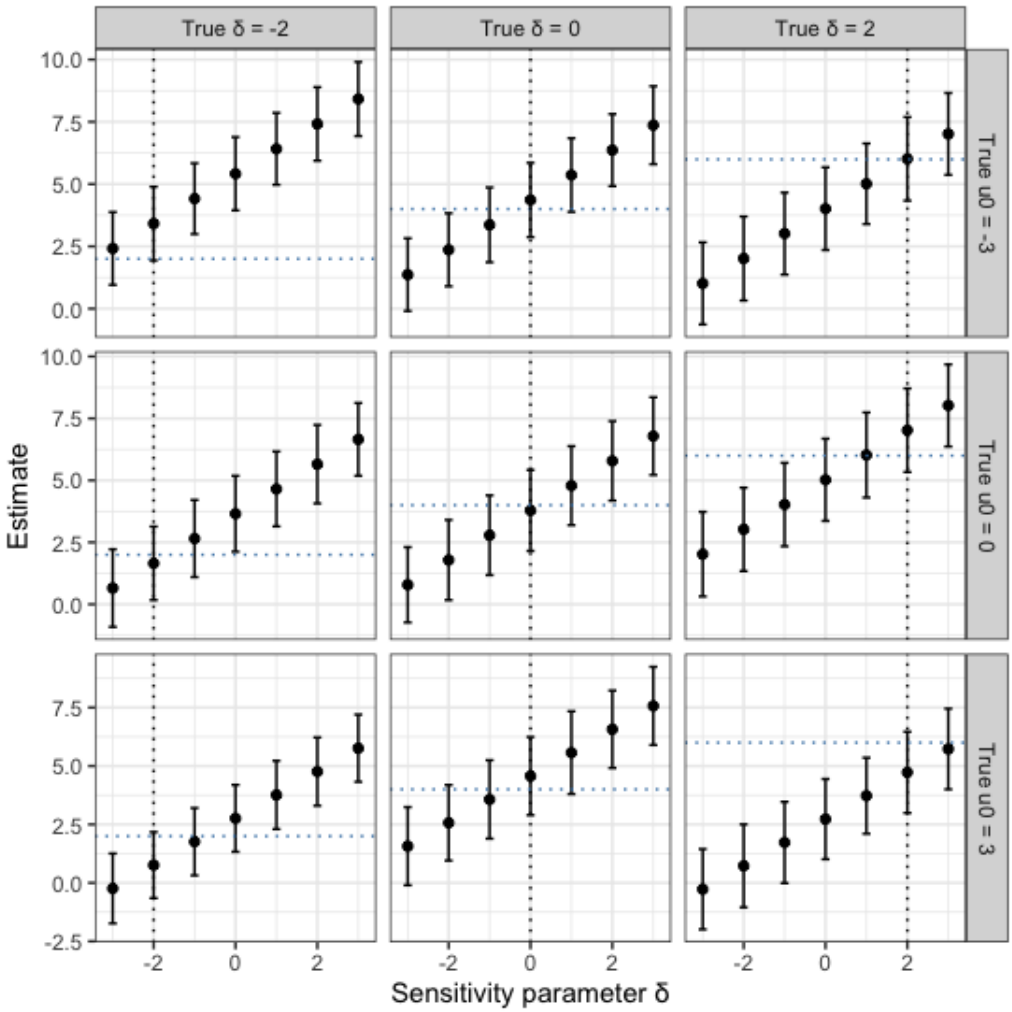

Figure 2: Sensitivity-parameter-adjusted ATE estimate shown against the true study-specific ATE in the study in which the outcome is unobserved across values of the true bias and sensitivity parameter; n=100 for each study, 95% CI constructed from 1000 bootstrap samples. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

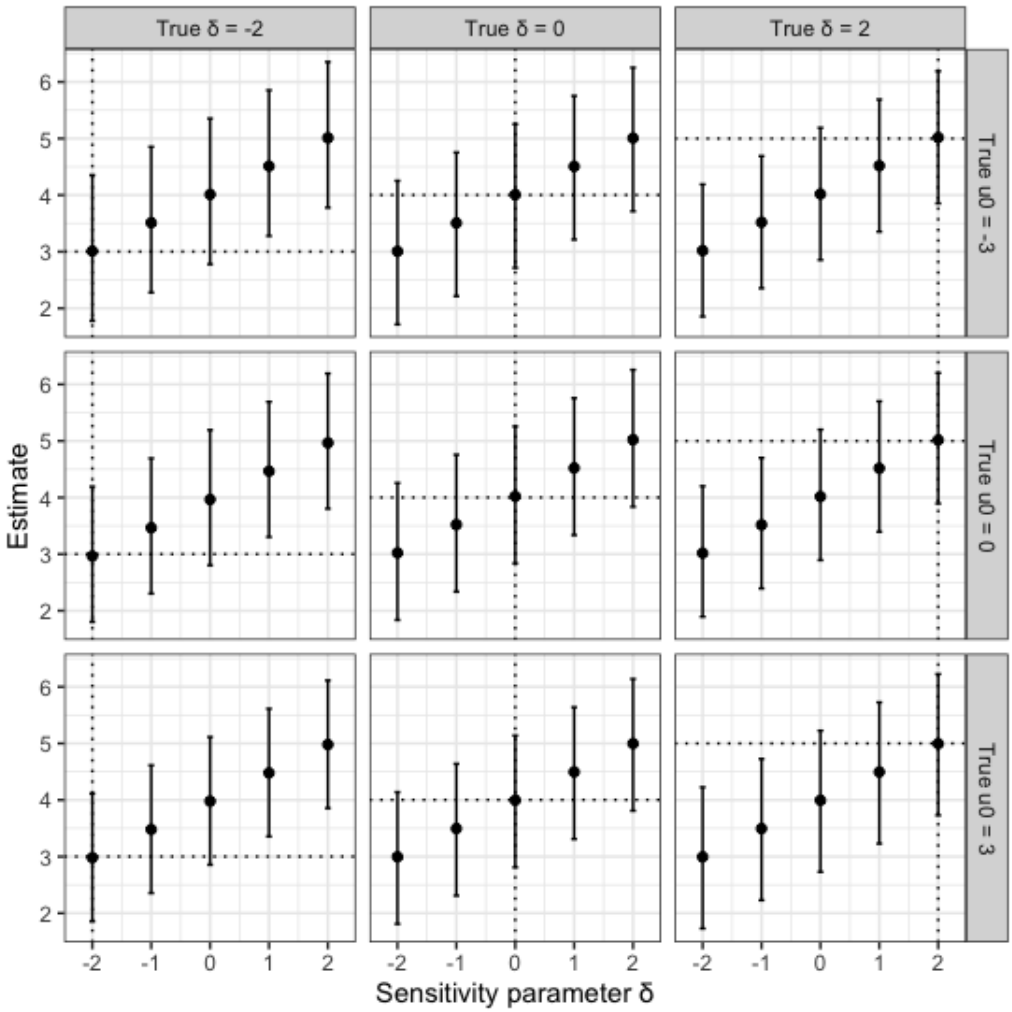

Figure 3: Sensitivity-parameter-adjusted ATE estimates shown against the true overall ATE across values of the true bias sensitivity parameter; mean, 2.5th and 97.5th quantiles obtained from 1000 simulations. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

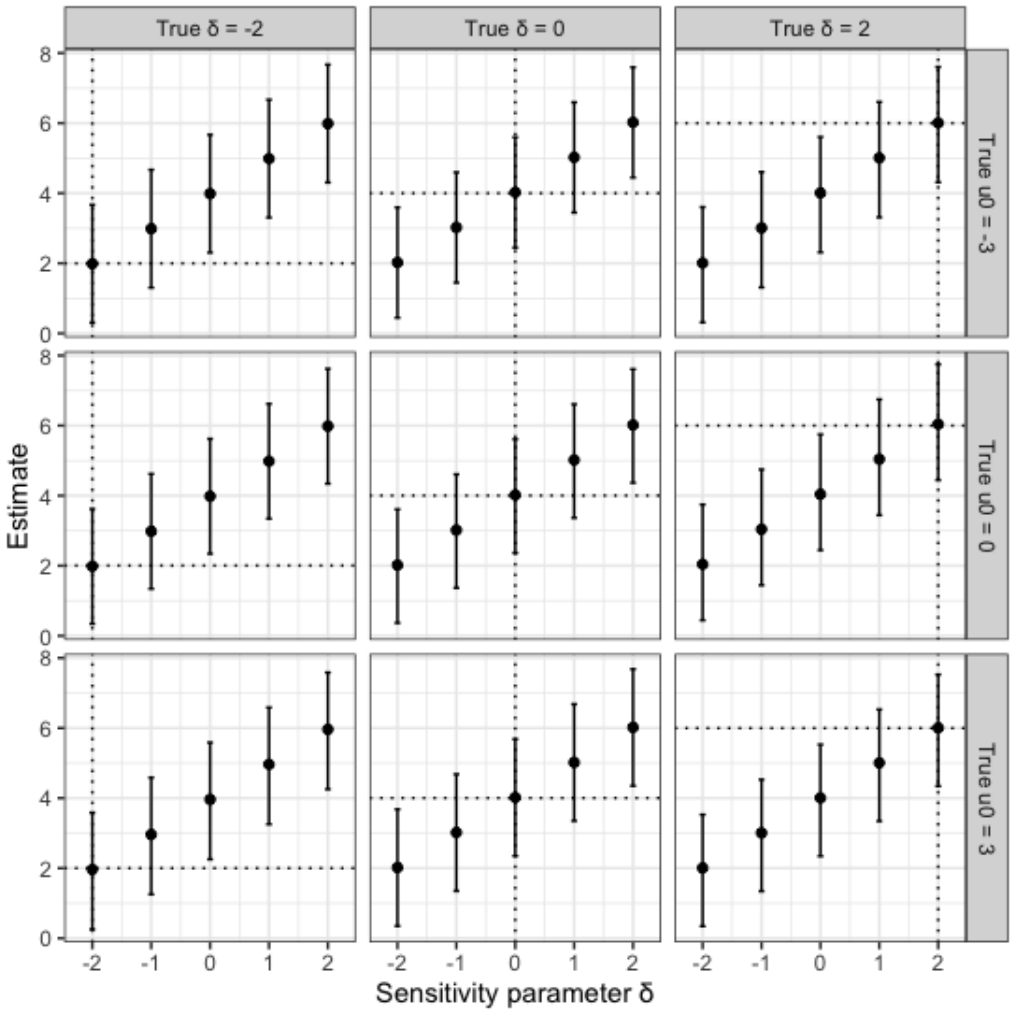

Figure 4: Sensitivity-parameter-adjusted ATE estimates shown against the true ATE in the study with missing outcome across values of the true bias and sensitivity parameter; mean, 2.5th and 97.5th quantiles obtained from 1000 simulations. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

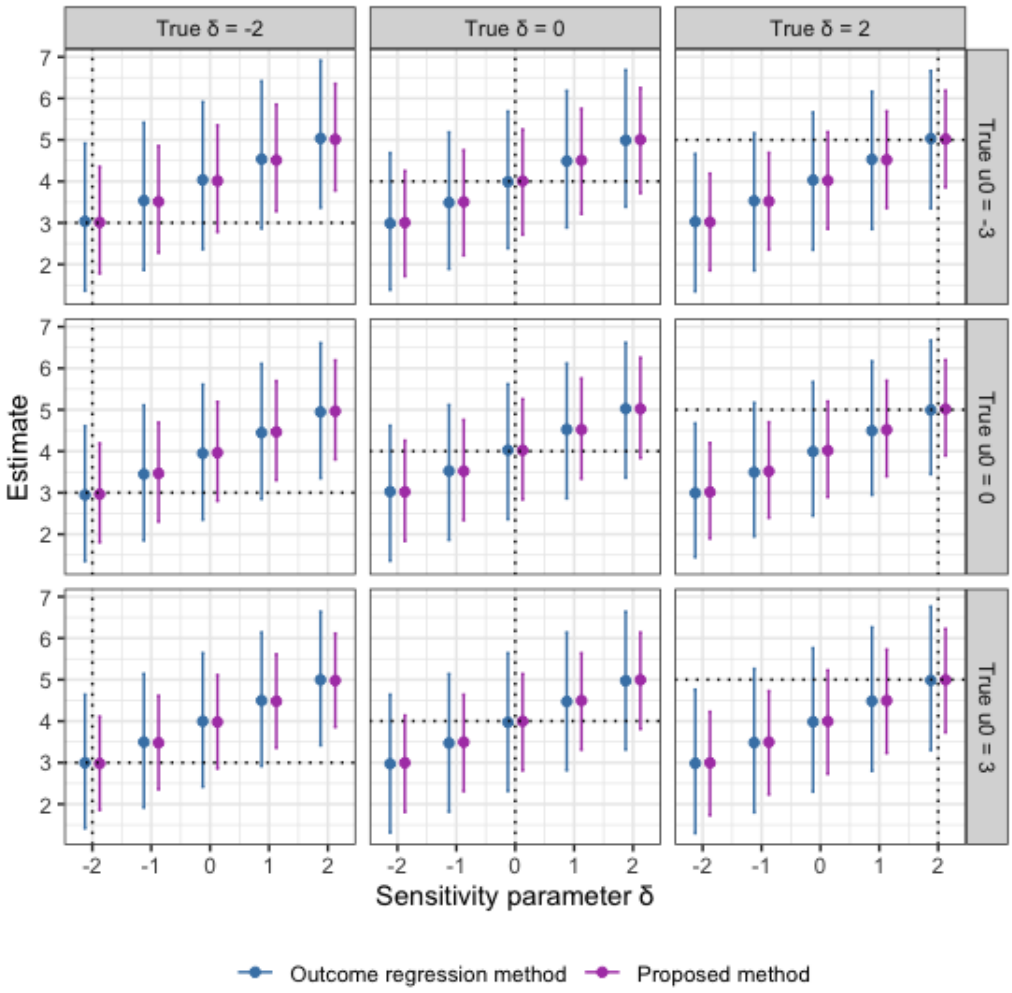

Figure 5: Sensitivity-parameter-adjusted ATE estimates obtained from our proposed method and the outcome regression method that does not utilize outcome proxies; mean, 2.5th and 97.5th quantiles obtained from 1000 simulations. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

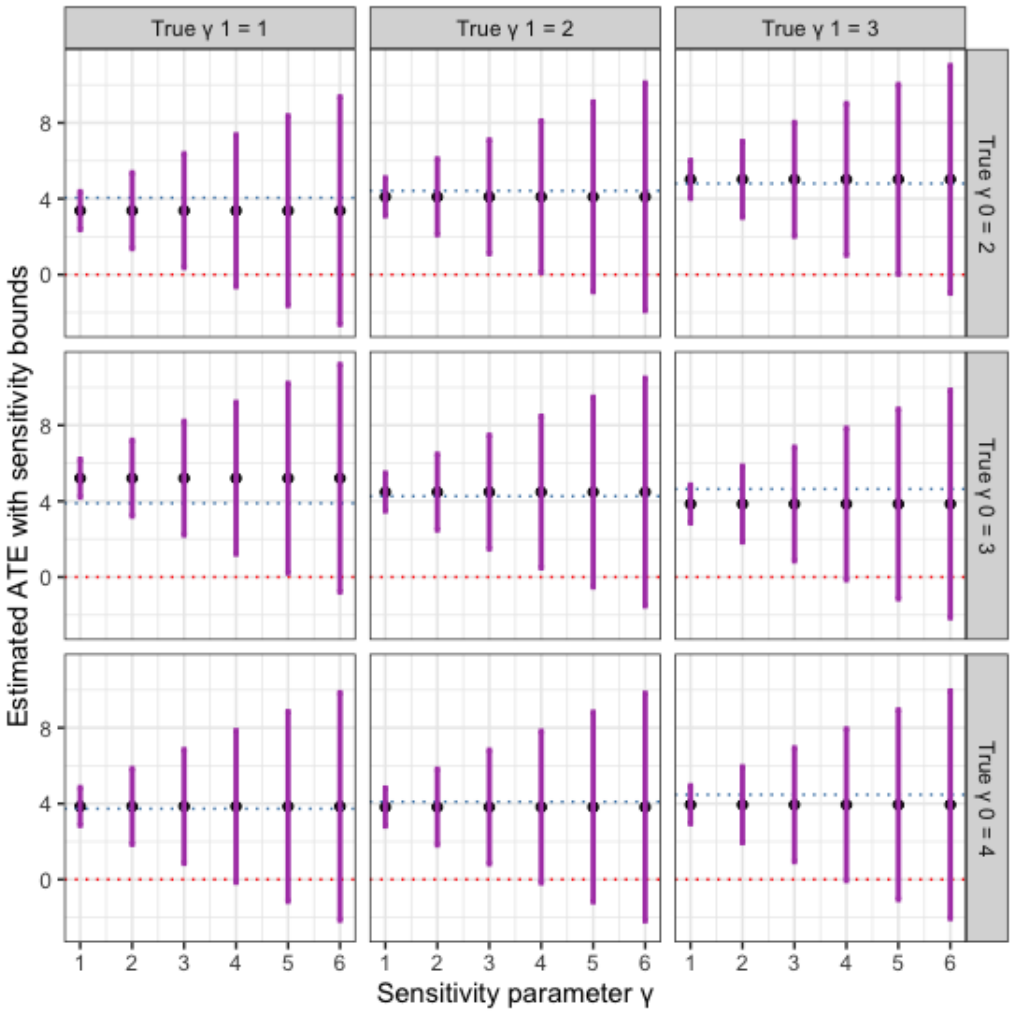

Figure 6: Bounded ATE estimates shown against the true overall ATE across values of the true bias and sensitivity parameter. Blue horizontal dotted line shows the true study-specific ATE given true bias functions

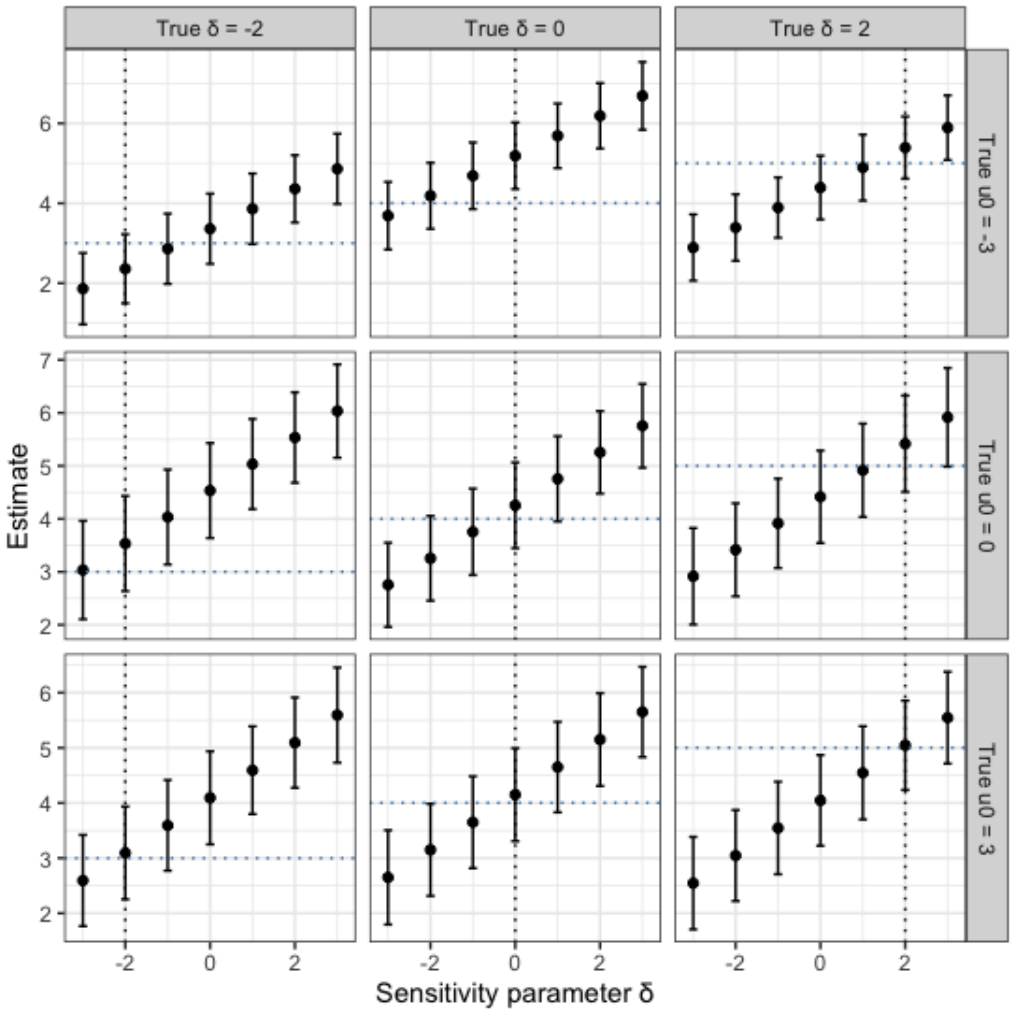

Figure 7: Bias-adjusted and unadjusted ATE estimate shown against the true overall ATE across values of the true bias and sensitivity parameter; n=200 for each study, 95% CI constructed from 1000 bootstrap samples. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

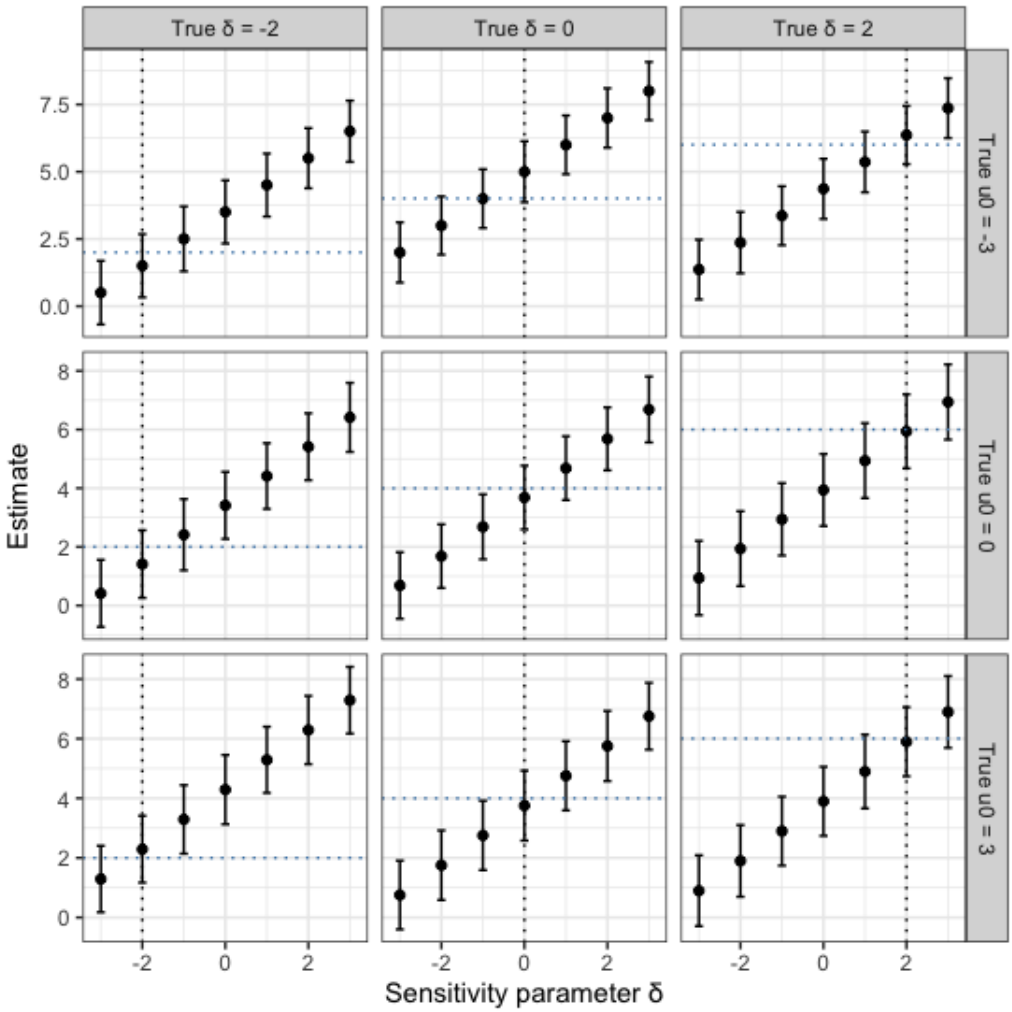

Figure 8: Bias-adjusted and unadjusted ATE estimate shown against the true ATE in the study with missing outcome across values of the true bias and sensitivity parameter; n=200 for each study, 95% CI constructed from 1000 bootstrap samples. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

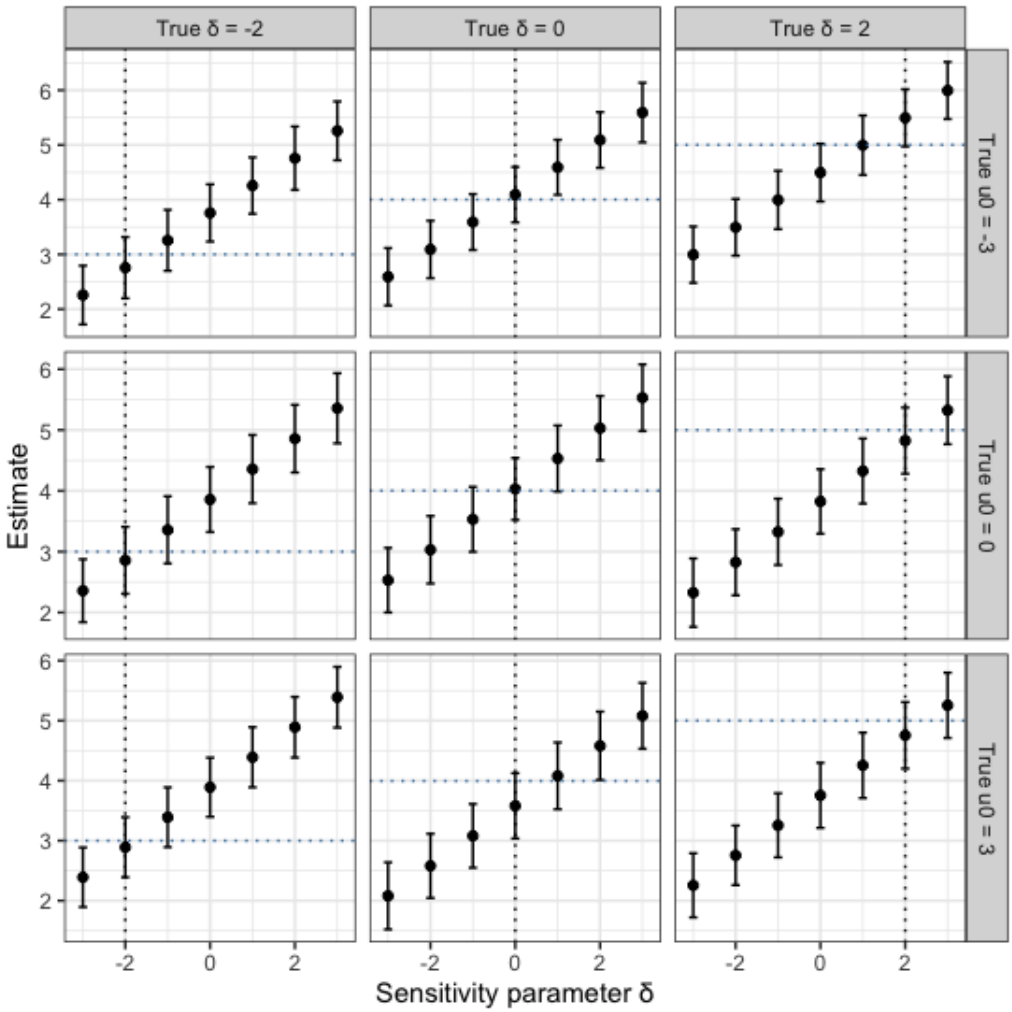

Figure 9: Bias-adjusted and unadjusted ATE estimate shown against the true overall ATE across values of the true bias and sensitivity parameter; n=500 for each study, 95% CI constructed from 1000 bootstrap samples. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

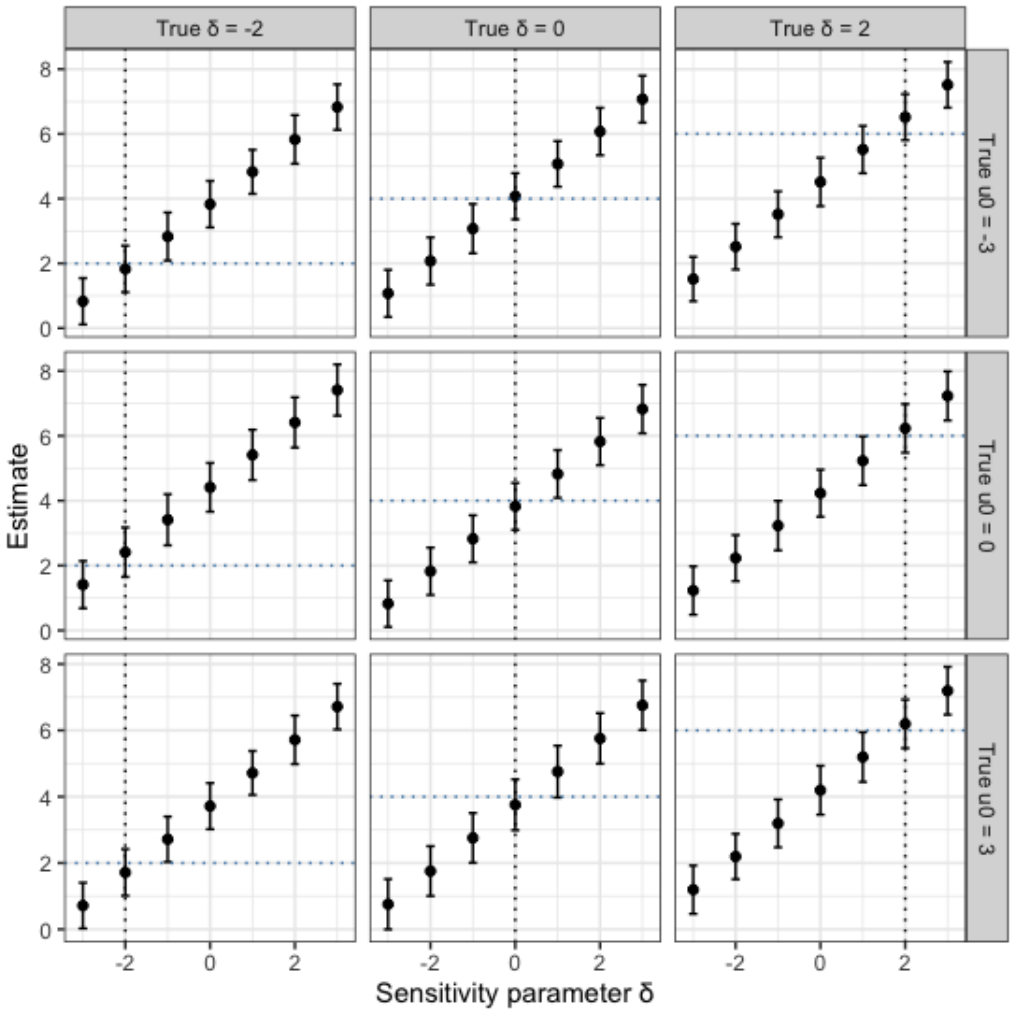

Figure 10: Bias-adjusted and unadjusted ATE estimate shown against the true ATE in the study with missing outcome across values of the true bias and sensitivity parameter; n=500 for each study, 95% CI constructed from 1000 bootstrap samples. Horizontal dotted line shows the true study-specific ATE given true δ; vertical dotted line indicates sensitivity parameter δ equals true δ

B Appendix

Derivation of the identification result when assumption (C4) is violated:

$$
\begin{aligned}
\text{ATE} = &\sum_{s=1}^{s^*} \pi_S E\{E(Y \mid W, A=1, S=s) - E(Y \mid W, A=0, S=s) \mid S=s\} \\
&+ \sum_{s=s^*+1}^{\text{S}} \pi_s E\left[E\left\{E\left(Y \mid T_s, W, A=1, S=s\right) \mid W, A=1, S=s\right\}\right. \\
&\qquad \left. - E\left\{E\left(Y \mid T_s, W, A=0, S=s\right) \mid W, A=0, S=s\right\} \mid S=s\right] \\
= &\sum_{s=1}^{s^*} \pi_S E\{E(Y \mid W, A=1, S=s) - E(Y \mid W, A=0, S=s) \mid S=s\} \\
&+ \sum_{s=s^*+1}^{\text{S}} \pi_s E\left[E\left\{E\left(Y \mid T_s, W, A=1, S \in \sigma_s\right) + u\left(A=1, T_s, W\right) \mid W, A=1, S=s\right\}\right. \\
&\qquad \left. - E\left\{E\left(Y \mid T_s, W, A=0, S \in \sigma_s\right) + u\left(A=0, T_s, W\right) \mid W, A=0, S=s\right\} \mid S=s\right] \\
= &\sum_{s=1}^{s^*} \pi_S E\{E(Y \mid W, A=1, S=s) - E(Y \mid W, A=0, S=s) \mid S=s) \\
&+ \sum_{s=s^*+1}^{\text{S}} \pi_s E\left[E\left\{E\left(Y \mid T_s, W, A=1, S \in \sigma_s\right) \mid W, A=1, S=s)\right\}\right. \\
&\qquad \left. -E\left\{E\left(Y \mid T_s, W, A=0, S \in \sigma_s\right) \mid W, A=0, S=s)\right\} \mid S=s\right] \\
&+ \sum_{s=s^*+1}^{\text{S}} \pi_s E[E\left\{u\left(A=1, T_s, W\right) \mid W, A=1, S=s\right\} \\
&\qquad - E\left\{u\left(A=0, T_S, W\right) \mid W, A=0, S=s\right\} \mid S=s]
\end{aligned}
$$