Using Post-Quality of Life Measurement Information in Censoring by Death Problems

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Summary. Many clinical studies on non-mortality outcomes such as quality of life suffer from the problem that the non-mortality outcome can be censored by death, i.e. the non-mortality outcome cannot be measured if the subject dies before the time of measurement. To address the problem that this censoring by death is informative, it is of interest to consider the average effect of the treatment on the non-mortality outcome among subjects whose measurement would not be censored under either treatment or control, called the survivor average causal effect (SACE). The SACE is not point identified under usual assumptions but informative bounds can be constructed. The previous literature on bounding the SACE use only the survival information before the measurement of the non-mortality outcome. However, survival information after the measurement of the non-mortality outcome could also be informative in many studies. For randomized trials, we propose a set of ranked average score assumptions that make use of survival information before and after the measurement of the non-mortality outcome which are plausibly satisfied in many studies and develop a two-step linear programming approach to obtain the closed form for bounds on the SACE under our assumptions. We also extend our method to randomized trials with noncompliance or observational studies with a valid IV to obtain bounds on the complier survivor average causal effect. We apply our method to a randomized trial study of the effect of mechanical ventilation with lower tidal volume vs. traditional tidal volume for acute lung injury patients. Our bounds on the SACE are much shorter than the bounds obtained using only the survival information before

the measurement of the non-mortality outcome.

1. Introduction

In many clinical studies, researchers are interested in the effect of a treatment on a non-mortality outcome such as complications or quality of life in addition to mortality. However, the assessment of the causal effect on non-mortality outcomes of interest is often complicated by censoring by death. This censoring by death occurs because, by the time the non-mortality outcome is measured, some patients have died and thus the non-mortality outcome cannot be measured or is not well defined for these dead patients. For example, suppose we want to study the effect on intraventricular hemorrhage (IVH) of premature babies being delivered in a high-level neonatal intensive care unit (NICU) vs. a lower-level NICU. IVH is rarely present at birth but usually occurs in the first several days of life (See Lee, 2013). If the baby died before being born (a fetal death) or shortly after birth, then whether the baby had IVH is not well-defined. Another example is that in cancer studies, quality of life outcomes that might be measured six months or a year after treatment like incidence of fatigue, myelosuppression and treatment side-effects (e.g., Motzer et al., 2013) are important outcomes considered to assess the efficacy of a treatment. However, patients may die before the measurement of the quality of life outcomes; for those patients, the quality of life outcomes are not well-defined. Censoring by death is typically informative – patients who die usually would have had worse quality of life than those who did not die even if the dead patients could have somehow been kept alive (Cox et al., 1992). Furthermore, those patients who are saved by a treatment are often sicker patients on average than those patients who would live under both treatment and control. Consequently, a direct comparison of the non-

mortality outcomes among the survivors in treatment vs. control would be biased. To address the fundamental problems that the non-mortality outcomes are not well defined for those who die before measurement and that the censoring of the measurement is informative, Rubin (2000), and Frangakis and Rubin (2002) proposed a well defined causal estimand – the survivor average causal effect (SACE) – which is the effect of treatment on the non-mortality outcome among patients who would survive under both treatment and control to the time point when the non-mortality outcome is measured.

Without strong untestable assumptions, the SACE is not point identified; however, with reasonable assumptions, we can obtain an interval in which SACE will lie. Zhang and Rubin (2003) discussed various assumptions (ranked average score assumptions) that can be made to bound the SACE, and derive large sample bounds in a randomized trial. Imai (2008) provided an alternative proof that the bounds obtained in Zhang and Rubin (2003) are sharp and generalized the proof to obtain sharp bounds on the quantile treatment effect. Chiba (2012) proposed a number of assumptions that are different from the ranked average score assumptions in Zhang and Rubin (2003) and derived the corresponding bounds. Another stream of work on drawing inference about the SACE is through sensitivity analysis procedures, for instance, Hayden et al. (2005), Egleston et al. (2007), and Chiba and VanderWeele (2011). A problem similar to censoring by death arises in evaluating the effect of vaccine vs. placebo on post-infection outcomes. Hudgens, Hoering and Self (2003) developed tests for the causal effect on viral load among the individuals who would be infected no matter whether they received the vaccine regimen or a placebo regimen. Gilbert, Bosch and Hudgens (2003) proposed a class of models indexed by an interpretable sensitivity parameter, where the SACE is identified given the sensitivity parameter.

In the previous literature on bounding the SACE, only the survival information before the measurement on the non-mortality outcome has been used. However,

survival information after measurement may be informative. In this paper, we develop a method to use both the survival information before and after the measurement of non-mortality to sharpen inferences on the SACE in the setup of randomized experiments. We will also present an extension of our method to bound the complier survivor average causal effect (CSACE) in a randomized trial with noncompliance or an observational study where an instrumental variable (IV) is available.

We will apply our method to the ARDSNet study, a randomized clinical trial on the effect of mechanical ventilation with lower tidal volumes vs. traditional tidal volumes for patients suffering from acute lung injury (The Acute Respiratory Distress Syndrome Network, 2000). The trial found evidence that lower tidal volumes reduce mortality. The investigators were also interested in assessing the effect of lower tidal volumes on a quality of life (QOL) outcome, whether the patient was able to breathe without assistance by day 28. In the data, both survival at day 28, when the QOL is measured, and whether the patient was ultimately discharged home alive, post-QOL measurement survival information, are recorded. Utilizing the post QOL measurement survival information in addition to the pre-QOL measurement survival information, we are able to substantially sharpen the bounds on the SACE for the effect of lower tidal volume on being able to breathe without assistance by day 28.

The rest of the paper is organized as follows. In section 2, we introduce notations and assumptions to set up the causal framework. In section 3, we present the derivations of the bounds of SACE and provide some numerical examples to compare the bounds derived with the bound using one set of assumptions in Zhang and Rubin (2003). We extend our method to IV settings in section 4. In section 5, we discuss how to check the plausibility of our assumptions for the "large sample" data as well as the sample data. We discuss the confidence intervals for bounds in section 6, and we apply our approach to the tidal volume study in section 7. Conclusions and discussions are presented in section 8.

2. Notations and Assumptions: Randomized Experiment with Perfect Compliance

In this section and the following, we focus on two arm randomized experiments where the subjects are randomly assigned to either treatment or control. The method is extended to IV settings in section 4.

2.1. Notations

We use the potential outcomes approach to define causal effects. Let D_i represent the binary treatment for the ith subject; we call level 1 "the treatment" and level 0 "the control". Let $\boldsymbol{D}$ denote the vector of treatment assignment indicators for all subjects. Let $S_{1i}(\boldsymbol{d})$ be the potential survival indicator of subject i that would be observed at the first time point after which the measurement of non-mortality outcome is taken, with 0 indicating death, 1 if alive. Let $Y_i(\boldsymbol{d})$ represent the potential non-mortality binary outcome (for instance, complication of babies, QOL of participants) that would be observed under treatment assignment $\boldsymbol{d}$. The non-mortality outcome is measured after the first time point, thus if the subject would die before that time point ($S_{1i}(\boldsymbol{d}) = 0$), $Y_i(\boldsymbol{d})$ is not defined. For convenience, we assume that level 1 of the non-mortality outcome is worse than level 0 of the outcome, e.g., in the ARDSNet study, level 1 indicates that the patient was not able to breathe without assistance by day 28 and level 0 indicates the patient was able to breathe without assistance by day 28. We further define $S_{2i}(\boldsymbol{d})$ to be the potential indicator of survival at the second time point for subject i that would be observed if under treatment assignment $\boldsymbol{d}$. If $S_{1i}(\boldsymbol{d}) = 0$, then $S_{2i}(\boldsymbol{d}) = 0$ by definition. We use D_i, S_{1i}, Y_i and S_{2i} to denote respectively the observed treatment received, observed survival indicator at the first time point, observed non-mortality outcome and observed survival indicator at the second time point for subject i.

2.2. Assumptions

We assume that the following assumptions hold for randomized experiments.

Assumption 1. Stable unit treatment value assumption (SUVTA).

- If $d_i = d_i'$, then $S_{1i}(\boldsymbol{d}) = S_{1i}(\boldsymbol{d}')$, $S_{2i}(\boldsymbol{d}) = S_{2i}(\boldsymbol{d}')$, and $Y_i(\boldsymbol{d}) = Y_i(\boldsymbol{d}')$

SUVTA means that there is no interference between subjects so that a subject's outcome only depends on the subject's own treatment. Under SUVTA, each subject has two potential first time point survival outcomes $(S_{1i}(1), S_{1i}(0))$, based on values of which we can classify subjects into four groups:

- $11 = \{i | S_{1i}(1) = 1, S_{1i}(0) = 1\}$, always survivors: the subjects that would survive at least to the first time point under both treatment arms,

- $10 = \{i | S_{1i}(1) = 1, S_{1i}(0) = 0\}$, protected: the subjects that would survive at least to the first time point under treatment, but would die before then under control;

- $01 = \{i | S_{1i}(1) = 0, S_{1i}(0) = 1\}$, harmed: the subjects that would die before the first time point under treatment, but would survive at least to the first time point under control;

- $00 = \{i | S_{1i}(1) = 0, S_{1i}(0) = 0\}$, never survivors: the subjects that would die before the first time point under both treatment arms;

Assumption 2. The assignment D_i of each subject is independent of his/her potential outcomes.

Assumption 3. Monotonicity: $S_{1i}(1) \geq S_{1i}(0), S_{2i}(1) \geq S_{2i}(0)$. There is no 01 (harmed) group.

The monotonicity assumption says that the treatment does not cause death, which is often plausible in practice. Under this assumption, subjects could either be "always survivors", "protected" or "never survivors". The most meaningful inference of causal effect of treatment on Y can be drawn only for the "always survivors",

Table 1. Fine Strata

Probability	$S_{1i}(1)$	$S_{1i}(0)$	$S_{2i}(1)$	$S_{2i}(0)$	Principal Strata at Time Point 1
π_{1111}	1	1	1	1	Always survivors
π_{1110}	1	1	1	0	Always survivors
π_{1100}	1	1	0	0	Always survivors
π_{1010}	1	0	1	0	Protected
π_{1000}	1	0	0	0	Protected
π_{0000}	0	0	0	0	Never survivors

because it is the only group for which both $Y_i(1)$ and $Y_i(0)$ are well defined, see Rubin (2000), Frangakis and Rubin (2002). Define the survivor average causal effect (SACE) as $\mathrm{E}(Y_i(1) - Y_i(0) \mid 11)$, which is our quantity of interest.

We further create finer strata based on the possible combinations of potential survival at both the first (QOL measurement point) and second (post-QOL measurement point) time points, which is described in Table 1.

The always survivors at time point 1 are divided into the following three subgroups: 1111, always survivors who would live at least to the second time point under both treatment arms; 1110, always survivors who would survive at least to the second time point under treatment, but would die before then under control; 1100, always survivors who although they can live at least to the first time point, would die before the second time point under both treatment arms. The protected at time point 1 are combinations of the following two subgroups: 1010, subjects who would live at least to the second time point under treatment, but would die before the first time point under control; 1000, subjects who if they receive treatment would live at least to the first time point but would die before the second time point, but if they receive control, would die even before the first time point. Never survivors comprise a single subgroup which we denote as 0000 because the second time point death indicator provides no additional information for them.

In terms of our fine strata, the SACE is expressed as:

$$SACE = \mathrm{E}(Y_i(1) - Y_i(0) \mid S_{1i}(1) = S_{1i}(0) = 1)$$

$$= P(Y_i(1) = 1 \mid S_{1i}(1) = S_{1i}(0) = 1) - P(Y_i(0) = 1 \mid S_{1i}(1) = S_{1i}(0) = 1)$$

$$= \frac{(\pi_{1111}\mathrm{E}(Y_i(1) \mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1) \mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1) \mid 1100))}{\pi_{1111} + \pi_{1110} + \pi_{1100}}$$

$$- \frac{(\pi_{1111}\mathrm{E}(Y_i(0) \mid 1111) + \pi_{1110}\mathrm{E}(Y_i(0) \mid 1110) + \pi_{1100}\mathrm{E}(Y_i(0) \mid 1100))}{\pi_{1111} + \pi_{1110} + \pi_{1100}} \tag{1}$$

Plausible assumptions can be made on data to tighten the bounds of SACE. Zhang and Rubin (2003) proposed the assumption that when assigned treatment, on average, the outcome for "always survivors" is better than "protected", in our case, that is to say $P(Y_i(1) = 1 \mid 11) \le P(Y_i(1) = 1 \mid 10)$, recalling that we use 1 to denote worse outcome for Y. This uses only the information on death before the measurement of the non-mortality outcome. In the rest of this paper, we will refer to this assumption as the ranked average score with one stage survival information assumption. Survival information after measurement of the non-mortality outcome may deliver finer information, making use of which can help us make more reasonable assumptions and sharpen inferences. We will refer to the following set of assumptions as ranked average score with two stage survival information assumptions.

Assumption 4. Among always survivors at time point 1, the probability of worse outcome for group 1111 is the lowest, whereas the probability of worse outcome for group 1100 is the highest under both treatment arms:

$$P(Y_i(1) = 1 \mid 1111) \le P(Y_i(1) = 1 \mid 1110) \le P(Y_i(1) = 1 \mid 1100) \tag{2}$$

$$P(Y_i(0) = 1 \mid 1111) \le P(Y_i(0) = 1 \mid 1110) \le P(Y_i(0) = 1 \mid 1100) \tag{3}$$

Assumption 5. Among protected at time point 1, the probability of worse outcome for group 1010 is no higher than that for group 1000 under treatment:

$$P(Y_i(1) = 1 \mid 1010) \le P(Y_i(1) = 1 \mid 1000) \tag{4}$$

Assumption 6. Under treatment, the probability of worse outcome for group 1100 is not lower than that for group 1010, but not higher than that for group 1000,

and the probability of worse outcome for group 1110 is not higher than that for group 1010:

$$P(Y_i(1) = 1 \mid 1110) \leq P(Y_i(1) = 1 \mid 1010) \leq P(Y_i(1) = 1 \mid 1100) \leq P(Y_i(1) = 1 \mid 1000)$$

(5)

Assumptions 4, 5 and 6 are plausibly satisfied in many QOL studies. Consider the ARDSNet study of the effect of lower tidal volumes (treatment) vs. traditional tidal volumes (control) on being able to breathe without assistance by day 28 in the ICU described in the introduction, where the post-QOL measurement survival time point is being discharged home alive. Assumption 4 says, among patients who would survive to day 28 under both treatment and control, those patients who would be discharged home alive under both treatment and control are healthiest at day 28 on average, and those who would be discharged home alive under treatment but not control are healthier at day 28, than those who would die in the hospital under both treatment and control. Assumption 5 says, among patients who would survive to day 28 only under treatment, those patients who would ultimately be discharged home alive under treatment are healthier on average than patients who would ultimately die in the hospital. Assumptions 4 and 5 are plausible because being discharged home alive is a proxy for health at day 28. Assumption 6 is a comparison of the 1010 patients who would die before day 28 under control but survive to day 28 and be discharged home alive under treatment, to the 1100 patients who would survive to day 28 under both treatment and control but die in the hospital after day 28 under both treatment and control. Assumption 6 says that under the treatment, the 1010 patients tend to be healthier than the 1100 patients at day 28. This is plausible for the ARDSNet study for the following reasons. The 1100 patients are likely to be fairly sick by day 28 under the treatment since these patients will die in the ICU. In contrast, the 1010 patients are likely to be less sick on day 28 under the treatment because they will be (or already have) discharged home alive. An example of a 1010 patient would be a patient who was healthy but suffered a gunshot

wound that caused an acute lung injury. When the patient arrives at the ICU, the patient is in critical condition and only the treatment will save the patient, but if the patient receives the treatment, the patient's health before the gunshot wound will enable the patient to recover well and be regaining his or her health by day 28. In summary, assumptions 4, 5 and 6 are plausible for the ARDSNet study.

The ranked average score with one stage survival information assumption is different from our ranked average score with two stage survival information assumptions. The major difference is that the one-stage survival assumption assumes that always survivors, on average, have better QOL outcome than the protected, whereas our two-stage survival assumptions assume that one particular always survivors group, 1100, has worse QOL outcome than a particular protected group, 1010, on average under treatment, which is a more reasonable assumption for the ARDSNet study. The differences in the bounds obtained under the ranked average score with one stage survival information assumption and our two stage survival information assumptions are presented in numerical examples and the analysis of ARDSNet study in section 3.3 and 7 respectively.

3.   Derivations of Bounds

Under assumptions 1-6, the SACE is not point identified based on the knowledge of the observable joint distribution of $(D_i, S_{1i}, S_{2i}, Y_i)$. However, we can use that joint distribution to obtain an interval in which the SACE must lie. We first derive the bounds for the proportions in each stratum, then for fixed proportions we derive the bounds for the SACE. In this section, we assume that the joint distribution of $(D_i, S_{1i}, S_{2i}, Y_i)$ is known; in section 6, we will discuss forming confidence intervals for the bounds that acknowledge sample uncertainty. .

3.1. *Bounds for proportions of each stratum*

Notice that the observable strata of (D_i, S_{1i}, S_{2i}) are mixtures of fine strata (Table 1). Thus we can express the proportions of strata of (D_i, S_{1i}, S_{2i}) by proportions of fine strata. Combining this with the fact that all the proportions in the fine strata must lie between 0 and 1, we can obtain the bounds for each fine stratum's proportion. We use $p_{s_1 s_2 | d}$ to denote $P(S_{1i} = s_1, S_{2i} = s_2 \mid D_i = d)$. The following equations hold:

$$p_{11|1} = \pi_{1111} + \pi_{1110} + \pi_{1010} \tag{6}$$

$$p_{10|1} = \pi_{1100} + \pi_{1000} \tag{7}$$

$$p_{00|1} = \pi_{0000} \tag{8}$$

$$p_{11|0} = \pi_{1111} \tag{9}$$

$$p_{10|0} = \pi_{1110} + \pi_{1100} \tag{10}$$

$$p_{00|0} = \pi_{1010} + \pi_{1000} + \pi_{0000} \tag{11}$$

Further we have,

$$0 \le \pi_{1111}, \pi_{1110}, \pi_{1100}, \pi_{1010}, \pi_{1100}, \pi_{1000}, \pi_{0000} \le 1 \tag{12}$$

Given (6)-(11), we can express each π by functions of $p_{ss|d}$ and π_{1100}:

$$\pi_{1111} = p_{11|0}$$

$$\pi_{1110} = p_{10|0} - \pi_{1100}$$

$$\pi_{1010} = p_{11|1} - p_{11|0} - p_{10|0} + \pi_{1100}$$

$$\pi_{1000} = p_{10|1} - \pi_{1100}$$

$$\pi_{0000} = p_{00|1}$$

and subject to the constraint of (12), we have,

$$max\{0, p_{11|0} + p_{10|0} - p_{11|1}\} \le \pi_{1100} \le min\{p_{10|0}, p_{10|1}\} \tag{13}$$

3.2. Bounds for the SACE

In this step, we first derive the bounds for the SACE with known proportions of each fine stratum, then will combine the result with the bounds obtained in section 3.1 to construct the final bounds for the SACE.

The observable strata of $(Y_i, S_{1i}, S_{2i} \mid D_i)$ are mixtures of potential outcomes from the fine strata. Letting $q_{ys_1s_1|d}$ denote $P(Y_i = y, S_{1i} = s_1, S_{2i} = s_2 \mid D_i = d)$, we have the following identities:

$$q_{111|1} = \pi_{1111}E(Y_i(1) \mid 1111) + \pi_{1110}E(Y_i(1) \mid 1110) + \pi_{1010}E(Y_i(1) \mid 1010) \tag{14}$$

$$q_{110|1} = \pi_{1100}E(Y_i(1) \mid 1100) + \pi_{1000}E(Y_i(1) \mid 1000) \tag{15}$$

$$q_{111|0} = \pi_{1111}E(Y_i(0) \mid 1111) \tag{16}$$

$$q_{110|0} = \pi_{1110}E(Y_i(0) \mid 1110) + \pi_{1100}E(Y_i(0) \mid 1100) \tag{17}$$

Recall that

$$SACE = \frac{(\pi_{1111}E(Y_i(1) \mid 1111) + \pi_{1110}E(Y_i(1) \mid 1110) + \pi_{1100}E(Y_i(1) \mid 1100))}{\pi_{1111} + \pi_{1110} + \pi_{1100}}$$
$$- \frac{(\pi_{1111}E(Y_i(0) \mid 1111) + \pi_{1110}E(Y_i(0) \mid 1110) + \pi_{1100}E(Y_i(0) \mid 1100))}{\pi_{1111} + \pi_{1110} + \pi_{1100}} \tag{18}$$

Given $\pi's$, $\frac{(\pi_{1111}E(Y_i(0)|1111)+\pi_{1110}E(Y_i(0)|1110)+\pi_{1100}E(Y_i(0)|1100))}{\pi_{1111}+\pi_{1110}+\pi_{1100}} = \frac{q_{111|0}+q_{110|0}}{\pi_{1111}+\pi_{1110}+\pi_{1100}}$ which is point identified. Thus to bound the SACE, we only need to bound $\pi_{1111}E(Y_i(1) \mid 1111) + \pi_{1110}E(Y_i(1) \mid 1110) + \pi_{1100}E(Y_i(1) \mid 1100)$, which defines a linear programming problem:

$$\min / \max \quad (\pi_{1111}E(Y_i(1) \mid 1111) + \pi_{1110}E(Y_i(1) \mid 1110) + \pi_{1100}E(Y_i(1) \mid 1100)) \mid \pi_{1100} \tag{19}$$

Subject to:

$$q_{111|1} = \pi_{1111}E(Y_i(1) \mid 1111) + \pi_{1110}E(Y_i(1) \mid 1110) + \pi_{1010}E(Y_i(1) \mid 1010) \tag{20}$$

$$q_{110|1} = \pi_{1100}E(Y_i(1) \mid 1100) + \pi_{1000}E(Y_i(1) \mid 1000) \tag{21}$$

$$\mathrm{E}(Y_i(1) \mid 1111) \leq \mathrm{E}(Y_i(1) \mid 1110) \leq \mathrm{E}(Y_i(1) \mid 1100) \tag{22}$$

$$\mathrm{E}(Y_i(1) \mid 1010) \leq \mathrm{E}(Y_i(1) \mid 1000) \tag{23}$$

$$\mathrm{E}(Y_i(1) \mid 1110) \leq \mathrm{E}(Y_i(1) \mid 1010) \leq \mathrm{E}(Y_i(1) \mid 1100) \leq \mathrm{E}(Y_i(1) \mid 1000) \tag{24}$$

$$0 \leq \mathrm{E}(Y_i(1) \mid 1111), \mathrm{E}(Y_i(1) \mid 1110), \mathrm{E}(Y_i(1) \mid 1100), \mathrm{E}(Y_i(1) \mid 1010), \mathrm{E}(Y_i(1) \mid 1000) \leq 1 \tag{25}$$

where constraints (22)-(24) are imposed by assumptions 4-6.

The above linear programming problem has a solution if and only if $\frac{q_{110|1}}{p_{10|1}} \geq \frac{q_{111|1}}{p_{11|1}}$, which is an inequality that must be satisfied based on assumptions 4-6. For each possible value of π_{1100}, we solve the above linear programming problem; then, combining this result with the bound for π_{1100} derived in section 3.1 that $\pi_{1100} \in I$, where $I = [max\{0, p_{11|0} + p_{10|0} - p_{10|1}\}, \ min\{p_{10|0}, p_{10|1}\}]$, we have,

$$
\begin{aligned}
\min SACE &= \min_{\pi_{1100} \in I} \left[\frac{\min((\pi_{1111}\mathrm{E}(Y_i(1)\mid1111) + \pi_{1110}\mathrm{E}(Y_i(1)\mid1110) + \pi_{1100}\mathrm{E}(Y_i(1)\mid1100)) \mid \pi_{1100}) - (q_{111|0} + q_{110|0})}{\pi_{1111} + \pi_{1110} + \pi_{1100}} \right] \\
&= \begin{cases} max\{\frac{q_{111|1} + q_{110|1} - p_{11|1} - p_{10|1} + p_{11|0} + p_{10|0}}{p_{11|0} + p_{10|0}}, \frac{q_{111|1}}{p_{11|1}}\} - \frac{q_{111|0} + q_{110|0}}{p_{11|0} + p_{10|0}}, & \text{if } p_{11|0} + p_{10|0} - p_{11|1} \geq 0 \\ max\{0, \frac{q_{111|1}p_{10|1} + q_{110|1}(p_{11|0} + p_{10|0} - p_{11|1})}{p_{10|1}(p_{11|0} + p_{10|0})}\} - \frac{q_{111|0} + q_{110|0}}{p_{11|0} + p_{10|0}}, & \text{if } p_{11|0} + p_{10|0} - p_{11|1} < 0 \end{cases}
\end{aligned} \tag{26}
$$

$$
\begin{aligned}
\max SACE &= \max_{\pi_{1100} \in I} \left[\frac{\max((\pi_{1111}\mathrm{E}(Y_i(1)\mid1111) + \pi_{1110}\mathrm{E}(Y_i(1)\mid1110) + \pi_{1100}\mathrm{E}(Y_i(1)\mid1100)) \mid \pi_{1100}) - (q_{111|0} + q_{110|0})}{\pi_{1111} + \pi_{1110} + \pi_{1100}} \right] \\
&= \frac{q_{111|1}}{p_{11|1}} - \frac{q_{111|0} + q_{110|0}}{p_{11|0} + p_{10|0}} + \frac{q_{110|1}p_{11|1} - q_{111|1}p_{10|1}}{p_{10|1}p_{11|1}(p_{11|0} + p_{10|0})} \cdot min\{p_{10|0}, p_{10|1}\}
\end{aligned} \tag{27}
$$

The details of the calculation for the bounds of SACE are provided in the Appendix.

3.3. Numerical Examples

3.3.1. Example 1

Assume that the underlying truth about the population is described by Table 2. The SACE = 0.05, meaning that the treatment will increase the probability of the worse non-mortality outcome by 0.05 among always survivors who will survive at least to the first time point under both treatment and control.

Suppose that we have an infinite sample, then we would observe that

$$p_{11|1} = 0.65 \quad p_{10|1} = 0.2 \quad p_{00|1} = 0.15 \quad p_{11|0} = 0.5 \quad p_{10|0} = 0.15 \quad p_{00|0} = 0.35 \tag{28}$$

Table 2. Setup 1

% of population	Fine Strata	% of $Y_i(1) = 1$	% of $Y_i(0) = 1$
50	1111	10	5
10	1110	20	15
5	1100	40	35
5	1010	30	-
15	1000	50	-
15	0000	-	-

$$q_{111|1} = 0.085 \quad q_{110|1} = 0.095 \quad q_{111|0} = 0.025 \quad q_{110|0} = 0.0325 \tag{29}$$

Given the constraints imposed by the observed data (28)-(29) and assumptions 4-6, we obtain the bound for SACE: [0.042, 0.122], showing that the treatment increases the probability of the worse non-mortality outcome.

However, if we don't use the second time point survival information, the observed data would be:

$$P(S_{1i} = 1|D_i = 1) = 0.85 \quad P(S_{1i} = 1|D_i = 0) = 0.65 \tag{30}$$

$$P(Y_i = 1, S_{1i} = 1|D_i = 1) = 0.18 \quad P(Y_i = 1, S_{1i} = 1|D_i = 0) = 0.0575 \tag{31}$$

Then, given the constraints imposed by the observed data (30)-(31) and the ranked average score with one stage survival assumption, the bound we would obtain for the SACE is [-0.088, 0.123], according to which we wouldn't know whether or not the treatment increases the probability of the worse non-mortality outcome even though the true SACE is positive. From this example, we see that making use of the survival information after measurement may provide us with more information and narrow the bounds on the SACE.

3.3.2. Example 2

Through elementary calculation, one can easily prove that the lower bound for the SACE under our assumptions (4)-(6) will be at least equal to or larger than the lower

Table 3. Setup 2

% of population	Fine Strata	% of $Y_i(1) = 1$	% of $Y_i(0) = 1$
50	1111	10	5
15	1110	20	15
5	1100	40	35
5	1010	30	-
10	1000	50	-
15	0000	-	-

bound for SACE under the ranked average score with one stage survival information assumption. However, the upper bound under our two stage survival information assumption is not comparable with the upper bound under one-stage survival assumption. Our upper bound can be smaller as shown in Example 1, but it can also be larger as we show below. Assume that the underlying truth about the population is described by the following Table 3.

The true SACE is 0.05. If we have an infinite sample, then we would have the following observed data:

$$p_{11|1} = 0.7 \quad p_{10|1} = 0.15 \quad p_{00|1} = 0.15 \quad p_{11|0} = 0.5 \quad p_{10|0} = 0.2 \quad p_{00|0} = 0.3 \quad (32)$$

$$q_{111|1} = 0.095 \quad q_{110|1} = 0.07 \quad q_{111|0} = 0.025 \quad q_{110|0} = 0.04 \quad (33)$$

Given the constraints imposed by the observed data (32)-(33) and assumptions 4-6, we obtain the bounds for the SACE: [0.043, 0.114]. If we don't utilize the second time survival information, we would observe the following data:

$$P(S_{1i} = 1 | D_i = 1) = 0.85 \quad P(S_{1i} = 1 | D_i = 0) = 0.7 \quad (34)$$

$$P(Y_i = 1, S_{1i} = 1 | D_i = 1) = 0.165 \quad P(Y_i = 1, S_{1i} = 1 | D_i = 0) = 0.065 \quad (35)$$

Then, given the constraints imposed by the observed data (34)-(35) and the ranked average score with one stage survival information assumption, the bound we would

obtain for the SACE is [-0.071, 0.101]. In this setup, the upper bound under the ranked average score with two stage survival information assumption (Assumption 4-6) is larger than that of the ranked average score with one stage survival information assumption. The reason is that the ranked average score with two stage survival information assumptions allow for the possibility that the always survivors' (1111, 1110, 1100) probability of bad outcome exceed the protecteds' (1010, 1000) probability of bad outcome which contradicts the ranked average score with one stage survival information assumption.

4. Extension to IV settings

The idea of using second time point survival information to sharpen the inference of SACE under randomized trials with perfect compliance can be naturally extended to randomized trials with noncompliance or observational studies with a valid IV to obtain inference about the complier survivor average causal effect (CSACE). In a randomized trial with noncompliance, the assignment of treatment can be used as an IV to assess the effects of receiving the treatment on the outcome. In observational studies, natural experiments such as a person's draft lottery number, randomly assigned federal judges or quarter of birth have been used as IVs. (Angrist, 1990; Angrist and Krueger, 1991; Kling, 1999). For more literatures on IV, see Angrist, Imbens, and Rubin (1996), Abadie (2002), Hernan and Robins (2006), Tan (2006), Brookhart and Schneeweiss (2007), Cheng (2009), and Clarke and Windmeijer (2012).

Let Z_i represent the binary IV; 1 encourages the treatment for the ith subject and 0 does not provide encouragement of the treatment. We use $\boldsymbol{Z}$ to denote the vector of IV for all subjects. Let $D_i(\boldsymbol{z})$ be the potential binary treatment variable that would be observed under IV assignment $\boldsymbol{z}$ for subject i; 1 being the treatment and 0 denotes the control. Let $S_{1i}(\boldsymbol{z})$ be the potential survival indicator of subject i that would be observed at the first time point after which the measurement of non-

mortality outcome is taken; with 0 indicating death, 1 if alive. Let $Y_i(\boldsymbol{z})$ represent the potential non-mortality binary outcome that would be observed under IV assignment $\boldsymbol{z}$. Again, the non-mortality outcome would be measured after the first time point, thus if the subject would die before that time point ($S_{1i}(\boldsymbol{z}) = 0$), $Y_i(\boldsymbol{z})$ is not defined; otherwise $S_{1i}(\boldsymbol{z}) = 1$ and $Y_i(z) = 1$ or 0, 1 indicating a worse outcome. We further define $S_{2i}(\boldsymbol{z})$ to be the potential indicator of survival at the second time point for subject i that would be observed if under IV assignment $\boldsymbol{z}$. As in section 2, if $S_{1i}(\boldsymbol{z}) = 0$, then $S_{2i}(\boldsymbol{z}) = 0$ by definition. We use Z_i, D_i, S_{1i}, Y_i and S_{2i} to denote respectively the observed IV, treatment received, observed survival indicator at the first time point, observed non-mortality outcome and observed survival indicator at the second time point for subject i.

4.1. Assumptions

We assume the following assumptions hold for the IV setup. These assumptions combine those of Angrist, Imbens and Rubin (1996) for the IV setup and the ranked average score with two stage survival information assumptions of section 2.

Assumption IV-1. Stable unit treatment value assumption (SUVTA).

- If $z_i = z_i'$, then $D_i(\boldsymbol{z}) = D_i(\boldsymbol{z}')$, $S_{1i}(\boldsymbol{z}) = S_{1i}(\boldsymbol{z}')$, $S_{2i}(\boldsymbol{z}) = S_{2i}(\boldsymbol{z}')$, and $Y_i(\boldsymbol{z}) = Y_i(\boldsymbol{z}')$

SUVTA means that a subject's potential treatments and outcomes are not affected by other individuals' IV status and means that we can write $D_i(\boldsymbol{z})$ as $D_i(z_i)$, $S_{1i}(\boldsymbol{z})$ as $S_{1i}(z_i)$, $S_{2i}(\boldsymbol{z})$ as $S_{2i}(z_i)$ and $Y_i(\boldsymbol{z})$ as $Y_i(z_i)$

Assumption IV-2. Nonzero average causal effect of Z on D. The average causal effect of Z on D, $\mathrm{E}[D_i(1) - D_i(0)]$, is not equal to zero.

Assumption IV-3. Independence of the instrument from unmeasured confounders: the random vector $(D(1), D(0), S_1(1), S_1(0), S_2(1), S_2(0), Y(1), Y(0))$ is independent of Z.

Based on subjects' compliance behavior, we can first partition the population into four groups:

$$U_i = \begin{cases} 00, & \text{if } D_i(1) = D_i(0) = 0 \\ 10, & \text{if } D_i(1) = 1, \ D_i(0) = 0 \\ 11, & \text{if } D_i(1) = D_i(0) = 1 \\ 01, & \text{if } D_i(1) = 0, \ D_i(0) = 1 \end{cases} \tag{36}$$

where 00, 10, 11, and 01 represent never taker, complier, always taker and defier, respectively. Because $D_i(1)$ and $D_i(0)$ are never observed jointly, the compliance behavior of a subject is unknown.

Assumption IV-4. Monotonicity of effect of IV on treatment: $D(1) \geq D(0)$. There is no U=01 group.

Assumption IV-5. Monotonicity of effect of IV on survival: $S_{1i}(1) \geq S_{1i}(0), S_{2i}(1) \geq S_{2i}(0)$.

The monotonicity of the effect of the IV on the survival will hold if the treatment never causes death and assumption IV-4 holds if the IV has a monotone effect on treatment.

Assumption IV-6. Exclusion restrictions among never-takers and always-takers:

$S_{1i}(1) = S_{1i}(0), S_{2i}(1) = S_{2i}(0), Y_i(1) = Y_i(0)$, for $U_i = 00$ or 11.

This means that the IV only affects the outcomes through treatment and has no direct effect on outcomes.

Based on the possible joint combinations of $(D_i(1), D_i(0), S_{1i}(1), S_{1i}(0))$ under the above assumptions, we can define principal strata as shown in Table 4.

Different from the case of randomized experiments with perfect compliance, the principal strata in the IV setup are defined with respect to IV levels, for example, the "complier, always survivors" are compliers(comply with their IV encouragement of treatment) who would survive under both IV levels. Among all the principal strata, the "complier, always survivors" (1011) group is the only group that we can observe

Table 4. Principal Strata

$D_i(1)$	$D_i(0)$	$S_{1i}(1)$	$S_{1i}(0)$	Principal Strata
1	0	1	1	Complier, always survivors
1	0	1	0	Complier, protected
1	0	0	0	Complier, never survivors
1	1	1	1	Never taker, always survivors
1	1	0	0	Never taker, never survivors
0	0	1	1	Always taker, always survivors
0	0	0	0	Always taker, never survivors

the outcome under treatment if IV is 1, as well as the outcome under control if IV is 0, and that would survive under both treatment such that the non-mortality outcome Y is well defined in both cases. Thus, it is the only group for which variation in the IV can identify the causal effect of the treatment on the non-mortality outcome: $CSACE = \mathrm{E}(Y_i(1) - Y_i(0) \mid 1011)$.

Similarly to the case of randomized experiments with perfect compliance (Section 2), we can further incorporate the information of second time survival indicator to create finer strata as shown in Table 5.

In terms of the fine strata in Table 5, the CSACE is expressed as:

$$
\begin{aligned}
CSACE &= \mathrm{E}(Y_i(1) - Y_i(0) \mid 1011) \\
&= P(Y_i(1) = 1 \mid 1011) - P(Y_i(0) = 1 \mid 1011) \\
&= \frac{(\pi_{101111}\mathrm{E}(Y_i(1) \mid 101111) + \pi_{101110}\mathrm{E}(Y_i(1) \mid 101110) + \pi_{101100}\mathrm{E}(Y_i(1) \mid 101100))}{\pi_{101111} + \pi_{101110} + \pi_{101100}} \\
&\quad - \frac{(\pi_{101111}\mathrm{E}(Y_i(0) \mid 101111) + \pi_{101110}\mathrm{E}(Y_i(0) \mid 101110) + \pi_{101100}\mathrm{E}(Y_i(0) \mid 101100))}{\pi_{101111} + \pi_{101110} + \pi_{101100}}
\end{aligned}
$$

$$(37)$$

The same assumptions are made for compliers as we made for subjects under randomized trials with perfect compliance (Assumptions 4-6 in Section 2).

Table 5. Fine Strata

Probability	$D_i(1)$	$D_i(0)$	$S_{1i}(1)$	$S_{1i}(0)$	$S_{2i}(1)$	$S_{2i}(0)$	Principal Strata at Time Point 1
π_{101111}	1	0	1	1	1	1	Complier, always survivors
π_{101110}	1	0	1	1	1	0	Complier, always survivors
π_{101100}	1	0	1	1	0	0	Complier, always survivors
π_{101010}	1	0	1	0	1	0	Complier, protected
π_{101000}	1	0	1	0	0	0	Complier, protected
π_{100000}	1	0	0	0	0	0	Complier, never survivors
π_{111111}	1	1	1	1	1	1	Always takers, always survivors
π_{111100}	1	1	1	1	0	0	Always takers, always survivors
π_{110000}	1	1	0	0	0	0	Always takers, never survivors
π_{001111}	0	0	1	1	1	1	Never takers, always survivors
π_{001100}	0	0	1	1	0	0	Never takers, always survivors
π_{000000}	0	0	0	0	0	0	Never takers, never survivors

Assumption IV-7. Among "complier, always survivors", the probability of worse outcome for group 101111 is the lowest, whereas the probability of worse outcome for group 101100 is the highest under both treatment arms:

$$P(Y_i(1) = 1 \mid 101111) \leq P(Y_i(1) = 1 \mid 101110) \leq P(Y_i(1) = 1 \mid 101100) \qquad (38)$$

$$P(Y_i(0) = 1 \mid 101111) \leq P(Y_i(0) = 1 \mid 101110) \leq P(Y_i(0) = 1 \mid 101100) \qquad (39)$$

Assumption IV-8. Among "complier, protected", the probability of worse outcome for group 101010 is no higher than that for group 101000 under treatment:

$$P(Y_i(1) = 1 \mid 101010) \leq P(Y_i(1) = 1 \mid 101000) \qquad (40)$$

Assumption IV-9. Under treatment, the probability of worse outcome for group 101100 is not lower than that for group 101010, but not higher than that for group 101000, and the probability of worse outcome for group 101110 is not higher than that for group 101010:

$$P(Y_i(1) = 1 \mid 101110) \le P(Y_i(1) = 1 \mid 101010) \le P(Y_i(1) = 1 \mid 101100) \le P(Y_i(1) = 1 \mid 101000)$$
(41)

4.2. Derivations of Bounds

As for the SACE in randomized experiments setup, the CSACE is not point identified without further assumptions based on the observable joint distribution of $(Z_i, D_i, S_{1i}, S_{2i}, Y_i)$, but can be bounded. We will again adopt the two step method we used in section 3 to obtain the bound.

4.2.1. Bounds for proportions of each stratum

The observable strata of $(Z_i, D_i, S_{1i}, S_{2i})$ are mixtures of fine strata, if we use $p_{s_1 s_2 d \mid z}$ to denote $P(S_{1i} = s_1, S_{2i} = s_2, D_i = d \mid Z_i = z)$, we have the following identities:

$$p_{111 \mid 1} = \pi_{101111} + \pi_{101110} + \pi_{101010} + \pi_{111111}$$
(42)

$$p_{101 \mid 1} = \pi_{101100} + \pi_{101000} + \pi_{111100}$$
(43)

$$p_{001 \mid 1} = \pi_{100000} + \pi_{110000}$$
(44)

$$p_{110 \mid 1} = \pi_{001111}$$
(45)

$$p_{100 \mid 1} = \pi_{001100}$$
(46)

$$p_{000 \mid 1} = \pi_{000000}$$
(47)

$$p_{110 \mid 0} = \pi_{101111} + \pi_{001111}$$
(48)

$$p_{100 \mid 0} = \pi_{101100} + \pi_{001100} + \pi_{101110}$$
(49)

$$p_{000|0} = \pi_{100000} + \pi_{000000} + \pi_{101010} + \pi_{101000} \tag{50}$$

$$p_{111|0} = \pi_{111111} \tag{51}$$

$$p_{101|0} = \pi_{111100} \tag{52}$$

$$p_{001|0} = \pi_{110000} \tag{53}$$

and the constraint

$$0 \le \pi_{101111}, \pi_{101110}, \pi_{101100}, \pi_{101010}, \pi_{101000}, \pi_{100000}, \pi_{111111}, \pi_{111100}, \pi_{110000}, \pi_{001111}, \pi_{001100}, \pi_{000000} \le 1 \tag{54}$$

Given (42)-(53), we can express each π in terms of $p_{s_1 s_2 d|z}$ and π_{101100}:

$$\pi_{000000} = p_{000|1}$$

$$\pi_{001111} = p_{110|1}$$

$$\pi_{001100} = p_{100|1}$$

$$\pi_{111111} = p_{111|0}$$

$$\pi_{110000} = p_{001|0}$$

$$\pi_{111100} = p_{101|0}$$

$$\pi_{100000} = p_{001|1} - p_{001|0}$$

$$\pi_{101111} = p_{110|0} - p_{110|1}$$

$$\pi_{101000} = p_{101|1} - p_{101|0} - \pi_{101100}$$

$$\pi_{101110} = p_{100|0} - p_{100|1} - \pi_{101100}$$

$$\pi_{101010} = p_{111|1} + p_{110|1} + p_{100|1} - p_{110|0} - p_{100|0} - p_{111|0} + \pi_{101100}$$

and subject to the constraint of (54), we have,

$$\max\{0, p_{110|0} + p_{100|0} + p_{111|0} - p_{111|1} - p_{110|1} - p_{100|1}\} \le \pi_{101100} \le \min\{p_{101|1} - p_{101|0}, p_{100|0} - p_{100|1}\} \tag{55}$$

4.2.2. Bounds for the CSACE

For fixed $\pi's$, let $q_{ys_1s_2d|z}$ denote $P(Y_i = y, S_{1i} = s_1, S_{2i} = s_2, D_i = d \mid Z_i = z)$. We have the following identities based upon the observable strata of $(Y_i, S_{1i}, S_{2i}, D_i, Z_i)$:

$$q_{1111|1} = \pi_{101111}E(Y_i(1) \mid 101111) + \pi_{101110}E(Y_i(1) \mid 101110) + \pi_{101010}E(Y_i(1) \mid 101010) + \pi_{111111}E(Y_i(1) \mid 111111) \tag{56}$$

$$q_{1101|1} = \pi_{101100}E(Y_i(1) \mid 101100) + \pi_{101000}E(Y_i(1) \mid 101000) + \pi_{111100}E(Y_i(1) \mid 111100) \tag{57}$$

$$q_{1110|1} = \pi_{001111}E(Y_i(1) \mid 001111) \tag{58}$$

$$q_{1100|1} = \pi_{001100}E(Y_i(1) \mid 001100) \tag{59}$$

$$q_{1111|0} = \pi_{111111}E(Y_i(0) \mid 111111) \tag{60}$$

$$q_{1101|0} = \pi_{111100}E(Y_i(0) \mid 111100) \tag{61}$$

$$q_{1110|0} = \pi_{101111}E(Y_i(0) \mid 101111) + \pi_{001111}E(Y_i(0) \mid 001111) \tag{62}$$

$$q_{1100|0} = \pi_{101110}E(Y_i(0) \mid 101110) + \pi_{101100}E(Y_i(0) \mid 101100) + \pi_{001100}E(Y_i(0) \mid 001100) \tag{63}$$

Recall that

$$CSACE = \frac{(\pi_{101111}E(Y_i(1) \mid 101111) + \pi_{101110}E(Y_i(1) \mid 101110) + \pi_{101100}E(Y_i(1) \mid 101100))}{\pi_{101111} + \pi_{101110} + \pi_{101100}}$$
$$- \frac{(\pi_{101111}E(Y_i(0) \mid 101111) + \pi_{101110}E(Y_i(0) \mid 101110) + \pi_{101100}E(Y_i(0) \mid 101100))}{\pi_{101111} + \pi_{101110} + \pi_{101100}}$$

$$\tag{64}$$

Given $\pi's$, $\frac{(\pi_{101111}E(Y_i(0)|101111) + \pi_{101110}E(Y_i(0)|101110) + \pi_{101100}E(Y_i(0)|101100))}{\pi_{101111} + \pi_{101110} + \pi_{101100}} = \frac{q_{1110|0} + q_{1100|0} - q_{1110|1} - q_{1100|1}}{\pi_{101111} + \pi_{101110} + \pi_{101100}}$ which is point identified. Thus to bound the CSACE, we only need to bound $\pi_{101111}E(Y_i(1) \mid 101111) + \pi_{101110}E(Y_i(1) \mid 101110) + \pi_{101100}E(Y_i(1) \mid 101100)$, which defines a linear programming problem:

$$\min/\max \quad (\pi_{101111}E(Y_i(1) \mid 101111) + \pi_{101110}E(Y_i(1) \mid 101110) + \pi_{101100}E(Y_i(1) \mid 101100)) \mid \pi_{101100}$$

$$\tag{65}$$

Subject to:

$$q_{1111|1} - q_{1111|0} = \pi_{101111}E(Y_i(1) \mid 101111) + \pi_{101110}E(Y_i(1) \mid 101110) + \pi_{101010}E(Y_i(1) \mid 101010)$$

$$\tag{66}$$

$$q_{1101|1} - q_{1101|0} = \pi_{101100}E(Y_i(1) \mid 101100) + \pi_{101000}E(Y_i(1) \mid 101000) \tag{67}$$

$$E(Y_i(1) \mid 101111) \le E(Y_i(1) \mid 101110) \le E(Y_i(1) \mid 101100) \tag{68}$$

$$E(Y_i(1) \mid 101010) \le E(Y_i(1) \mid 101000) \tag{69}$$

$$\text{E}(Y_i(1) \mid 101110) \le \text{E}(Y_i(1) \mid 101010) \le \text{E}(Y_i(1) \mid 101100) \le \text{E}(Y_i(1) \mid 101000) \qquad (70)$$

$$0 \le \text{E}(Y_i(1) \mid 101111), \text{E}(Y_i(1) \mid 101110), \text{E}(Y_i(1) \mid 101100), \text{E}(Y_i(1) \mid 101010), \text{E}(Y_i(1) \mid 101000) \le 1 \tag{71}$$

where constraints (68)-(70) are imposed by assumptions (IV-7) - (IV-9).

The above linear programming problem has a solution if and only if $\frac{q_{1101|1} - q_{1101|0}}{p_{101|1} - p_{101|0}} \ge \frac{q_{1111|1} - q_{1111|0}}{p_{111|1} - p_{111|0}}$.

For each possible value of π_{101100}, we can solve the above linear programming problem; then, combining this result with the bound for π_{101100} derived in section 4.2.1, let $L = p_{110|0} + p_{100|0} + p_{111|0} - p_{111|1} - p_{110|1} - p_{100|1}$, $U = \min\{p_{101|1} - p_{101|0}, p_{100|0} - p_{100|1}\}$, then $\pi_{101100} \in I$, where $I = [\max\{0, L\}, \ U]$, we obtain,

$$\min CSACE = \begin{cases} \max\{ \frac{q_{1111|1} - q_{1111|0} + q_{1101|1} - q_{1101|0} - p_{111|1} + p_{111|0} - p_{101|1} + p_{101|0} + p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1}}{p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1}}, \\ \frac{q_{1111|1} - q_{1111|0}}{p_{111|1} - p_{111|0}} \} - \frac{q_{1110|0} - q_{1110|1} + q_{1100|0} - q_{1100|1}}{p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1}}, & \text{if } L \ge 0 \\ \max\{0, \frac{(q_{1111|1} - q_{1111|0})(p_{101|1} - p_{101|0}) + (q_{1101|1} - q_{1101|0})(p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1} - p_{111|1} + p_{111|0})}{(p_{101|1} - p_{101|0})(p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1})} \} \\ - \frac{q_{1110|0} - q_{1110|1} + q_{1100|0} - q_{1100|1}}{p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1}}, & \text{if } L < 0 \end{cases} \tag{72}$$

$$\max CSACE = \frac{q_{1111|1} - q_{1111|0}}{p_{111|1} - p_{111|0}} - \frac{q_{1110|0} - q_{1110|1} + q_{1100|0} - q_{1100|1}}{p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1}}$$
$$+ \frac{(q_{1101|1} - q_{1101|0})(p_{111|1} - p_{111|0}) - (q_{1111|1} - q_{1111|0})(p_{101|1} - p_{101|0})}{(p_{101|1} - p_{101|0})(p_{110|0} - p_{110|1} + p_{100|0} - p_{100|1})(p_{111|1} - p_{111|0})} \cdot U \tag{73}$$

5. Checking the plausibility of ranked average score with two stage survival assumptions and exclusion restriction assumptions

From the observable data, it cannot be determined whether our ranked average score with two stage survival information assumptions for randomized experiments setup or IV settings hold, also it cannot be determined whether the exclusion restriction assumed in the IV settings hold. However, there are some necessary conditions that the probability distribution of the observable data must satisfy when these assumptions are valid. If these conditions are violated, then we know our assumptions

do not hold.

For randomized experiments with perfect compliance, from the derivation of the bound for SACE in section 3, we know that the linear programming problem (19)-(25) under the ranked average score with two stage survival information assumptions as well as the constraints imposed by the observable"infinite sample" probability distribution has a solution if and only if

$$\frac{q_{110|1}}{p_{10|1}} \geq \frac{q_{111|1}}{p_{11|1}} \tag{74}$$

This constraint says that the probability of the worse non-mortality outcome among the patients that are randomly assigned to treatment and that survive to the first time point but die before the second time point is equal to or larger than the probability of the worse non-mortality outcome among the patients that are randomly assigned to treatment and that survive at least to the second time point. This is a direct result from our ranked average score with two stage survival assumptions (Assumptions 4-6) which say that $E(Y_i(1) \mid 1111) \leq E(Y_i(1) \mid 1110) \leq E(Y_i(1) \mid 1010) \leq E(Y_i(1) \mid 1100) \leq E(Y_i(1) \mid 1000)$. The first three expectations are for subjects who can survive at least to the second time point under treatment and the last two expectations are for subjects who die before the second time point.

For the IV setting of Section 4, based on the calculations in section 4.2, the corresponding necessary conditions that the probability distribution of the data must satisfy under Assumptions (IV-1)-(IV-9) are as follows: ,

$$q_{1101|1} - q_{1101|0} \geq 0, \ p_{101|1} - p_{101|0} \geq 0, \ q_{1111|1} - q_{1111|0} \geq 0, \ p_{111|1} - p_{111|0} \geq 0 \tag{75}$$

$$\frac{q_{1101|1} - q_{1101|0}}{p_{101|1} - p_{101|0}} \geq \frac{q_{1111|1} - q_{1111|0}}{p_{111|1} - p_{111|0}} \tag{76}$$

Pearl (1995) provides a necessary condition on the joint probability distribution of the outcome, treatment and IV when the exclusion restriction holds. Extending

Pearl's result to our case where exclusion restrictions are assumed on both survival at the first time point and the second time point as well as a non-mortality outcome which may be censored, a necessary condition is that the following inequalities hold:

$$p_{00d|z_1} + q_{010d|z_2} + q_{110d|z_3} + q_{011d|z_4} + q_{111d|z_5} \leq 1 \tag{77}$$

where $d \in \{0, 1\}$, $z_i \in \{0, 1\}$ for $i = 1, 2, 3, 4, 5$

The above constraints to check the plausibility of our assumptions are for "infinite sample" data. In practice, we can estimate the confidence with which the true observable population distribution satisfies the above constraints using a simple bootstrap procedure (Efron and Tibshirani, 1998). We bootstrap from the empirical distribution of the observed data and then count the percentage of the bootstrapped data sets for which the empirical distribution satisfies the constraints as an estimate of the confidence. Efron and Tibshirani (1998) provide some refinements on this simple bootstrap procedure that improve the accuracy of the estimated confidence.

6.   Confidence Intervals for Bounds

In section 3 and 4, the bounds we obtained are "infinite sample" bounds where we assume that the joint distributions of $(D_i, S_{1i}, S_{2i}, Y_i)$ or $(Z_i, D_i, S_{1i}, S_{2i}, Y_i)$ is known. However, in practice, all these probabilities need to be estimated from the observed data. To account for the sampling uncertainty, we would like to construct confidence intervals for the bounds. The simplest way to construct confidence interval is through the Bonferroni method, where if we want an overall level of $1 - \alpha$, we can obtain first the individual $1 - \frac{\alpha}{2}$ confidence interval for the upper bound and lower bound (e.g., via the bootstrap), then combine the results to derive the simultaneous confidence interval. The disadvantage of the Bonferroni method is it's conservative; the way to form it ignores the joint distribution of the upper bound and lower

bound. Horowitz and Manski (2000) proposed a method to obtain the confidence interval taking into account the joint distribution of the lower and upper bound. The Horowitz and Manski confidence interval adds the same length to the upper and lower bounds in the confidence interval. Beran (1988) proposed the B method which also takes into account the joint distribution of upper and lower bounds without the restriction on the form of the confidence interval of the Horowitz and Manski confidence interval. A description of the above confidence interval approaches for bounds can be found in Cheng and Small (2006). Because of the nice properties of B method, we will use it to construct the confidence interval for the ARDSNet study.

We did a simulation study to examine the finite sample coverage of the B method 95% confidence interval for data like the ARDSNet study (See Section 7). We simulated 2000 samples based on the observed empirical distribution of the ARDSNet data (Table 6). Then for each simulated data set, we bootstrapped 2000 data sets to obtain the 95% B method confidence interval. We counted the proportion of the two thousand bootstrap CIs that cover the bound of the empirical distribution of the ARDSNet data and did the analysis using both the two stage and one stage assumptions. For the ranked average score with two stage survival information assumptions, the coverage probability of the B method is estimated to be 95.65%, and for the ranked average score with one stage survival information assumptions, the coverage probability of the B method is estimated to be 95.75%. Thus the finite sample coverage of the B method for studies like the ARDSNet study seems to be good.

7.   Application to ARDSNet Study

The ARDSNet study described in the introduction involved 861 patients with lung injury and acute respiratory distress syndrome who were randomized to receive mechanical ventilation with either lower tidal volumes or traditional tidal volumes. The non-mortality outcome variable we are interested in is whether patients were able

Table 6. Observed data for ARDSNet Study

Number of Patients	D_i	S_{1i}	S_{2i}	Y_i
258	1	1	1	0
29	1	1	1	1
10	1	1	0	0
26	1	1	0	1
109	1	0	0	–
211	0	1	1	0
34	0	1	1	1
7	0	1	0	0
25	0	1	0	1
152	0	0	0	–

to breathe without assistance by day 28 which is a measurement that reflects the quality of life for patients after treatment. We use Y_i to represent this binary quality of life measurement, with Y_i being 1 indicating that the ith patient were not able to breathe without assistance by day 28. Naturally, the first survival time point is day 28 after the treatment. If the patient died before day 28, then the non-mortality outcome could not be measured, thus will be undefined. The second time point survival indicator is whether the patient was eventually discharged home with unassisted breathing or not. We view the patients who received mechanical ventilation with lower tidal volume as the treatment group, and the patients who received mechanical ventilation with traditional tidal volume as the control group. Let D_i equal 1 if the ith patient is randomized to treatment group, 0 if randomized to control group. Further details on the data are described in appendix.

Table 6 presents the observed strata of $(D_i, S_{1i}, S_{2i}, Y_i)$. Among the survivors in the lower tidal volume group, the proportion of patients that cannot breathe without assistance by day 28 is 17.03% (which is 55/323); among the survivors in the traditional tidal volume group, the proportion of patients that cannot breathe without

Table 7. The estimated bounds and 95% B method CIs of the SACE for ARDSNet study using ranked average score with two stage survival assumptions and one stage survival assumptions.

SACE	Two-stage survival assumptions	One-stage survival assumptions
Estimated bounds	[−12.99%, −4.02%]	[−17.38%, −4.27%]
95% confidence interval	[−20.11%, 1.99%]	[−27.57%, 2.18%]

assistance by day 28 is 21.30% (which is 59/277). The difference of those two proportions −4.27% which is a direct comparison of the QOL among survivors in the lower tidal volume and survivors in the traditional tidal volume is likely an upward biased estimate for the SACE due to the informativeness of censoring by death.

The empirical distribution of $(D_i, S_{1i}, S_{2i}, Y_i)$ satisfies the constraint (74). Using the bootstrap procedure, all of the 2000 bootstrapped datasets satisfy the constraint (74), thus we are very confident that our set of two stage assumptions is plausible in the sense that it does not violate the constraint (74).

Table 7 compares the estimated bounds of the SACE as well as the 95% confidence intervals obtained through our proposed ranked average score with two stage survival information assumptions to the ranked average score with one stage survival information assumptions. According to the result of our two stage analysis, among the patients with lung injury and the acute respiratory distress syndrome who would survive under both ventilation tidal volumes, the lower tidal volume would help reduce the probability of breathing with assistance by day 28 by an amount between 4.02% to 12.99%. This bound for the SACE is substantially shorter, thus more informative, than the bound obtained through the one stage analysis which estimates the reduction to be between [4.27%, 17.38%]. The 95% B method confidence intervals under both sets of assumptions cover 0, meaning that there is not strong evidence that ventilation with lower tidal benefits patients in terms of the quality of life outcome of breathing without assistance by day 28.

8.   Conclusions and Discussions

The effect of treatment on a non-mortality outcome among always survivors is of interest in many clinical studies. The previous literature on bounding the SACE uses only the survival information before the measurement of the non-mortality outcome; however, in many cases, the survival information after the measurement of non-mortality outcome is informative. We proposed a set of ranked average score with two stage survival information assumptions which are plausibly satisfied in many quality of life studies and developed a two-step linear programming approach to obtain the closed form of the bounds of the SACE under our assumptions. Our method works not only for randomized trials with perfect compliance, but also can be extended to randomized trials with noncompliance or observational studies with a valid IV to obtain bounds on the complier survivor average causal effect.

We applied our method to the ARDSNet study. Making use of the post QOL measurement survival information (patients' status when discharged home) in addition to the pre-QOL survival information (survival status at day 28) helps substantially shorten the bound on the SACE – the effect of lower tidal volume on being able to breathe without assistance by day 28.

The SACE and CSACE are principal strata effects, causal effects on a subgroup of patients defined by the values that post-randomization variables would take under both treatment and control (Frangakis and Rubin, 2002). We have shown that bounds on these principal strata effects can be sharpened by using the further outcome information of survival after the non-mortality outcome is measured. In a different context, Mealli and Pacini (2013) showed that using further outcomes can narrow bounds on principal strata effects. Mealli and Pacini consider an outcome that is not affected by censoring by death in a randomized trial with noncompliance, and study bounds on the intention to treat effects for the compliers, always takers and never takers. Mealli and Pacini consider settings in which the exclusion restriction may not be satisfied and they show that a secondary outcome for which the

exclusion restriction is satisfied can be used to narrow the bounds. For randomized trials with noncompliance in which there is censoring by death and the exclusion restriction may not be satisfied, it would be of future research interest to consider combining the post-quality of life measurement survival information we have studied with the secondary outcomes Mealli and Pacini studied to narrow the bounds on the CSACE.

So far, we have assumed that we are in the context of a randomized trial or an observational study with a valid IV. Our method can also be naturally extended to the cases in which conditional on some discrete covariates there is ignorability such that the subjects are randomized or the IV is valid conditional on the covariates. We can stratify the subjects into subsets defined by each level of covariates, and apply our method to obtain the bound of SACE within each subgroup. Then we can obtain the overall bound of SACE combining the proportions of each subgroup. See (Freiman and Small, 2013) for more details on this topic. How to deal with the case in which the covariates are continuous requires further research.

In this study, we focus on studies where the non-mortality outcome is measured at a fixed time for all subject. However, there are cases where the non-mortality outcome might be measured at different time for different subjects which complicates the analysis. For instance, IVH may happen at any time in the first several days of life of babies. How to handle the situation in which the non-mortality outcome could be measured at continuous time period is a topic we are working on.

Acknowledgements:

Appendix:

A.   Bounds of the SACE

Given the value of π_{1100}, the linear programming problem (19)-(25) has a solution if and only if the set $\Phi = [\max\{q_{110|1} - \pi_{1000}, \frac{q_{111|1}\pi_{1100}}{\pi_{1111}+\pi_{1110}+\pi_{1010}}\}, \frac{q_{110|1}\pi_{1100}}{\pi_{1100}+\pi_{1000}}]$ is not empty, which is essentially $\frac{q_{110|1}}{p_{10|1}} \geq \frac{q_{111|1}}{p_{11|1}}$, an inequality that must be satisfied based on assumptions 4-6. If Φ is not empty, let $\underline{T} = \max\{q_{110|1} - \pi_{1000}, \frac{q_{111|1}\pi_{1100}}{\pi_{1111}+\pi_{1110}+\pi_{1010}}\}$, $\overline{T} = \frac{q_{110|1}\pi_{1100}}{\pi_{1100}+\pi_{1000}}$, the solution to the linear programming problem is,

$$\max((\pi_{1111}\mathrm{E}(Y_i(1) \mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1) \mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1) \mid 1100)) \mid \pi_{1100})$$
$$= \frac{q_{111|1}(\pi_{1111}+\pi_{1110})}{\pi_{1111}+\pi_{1110}+\pi_{1010}} + \overline{T} \tag{78}$$

$$\min((\pi_{1111}\mathrm{E}(Y_i(1) \mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1) \mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1) \mid 1100)) \mid \pi_{1100})$$
$$= \begin{cases} \underline{T} & \text{if } \frac{q_{111|1}\pi_{1100}}{\pi_{1010}} \leq \underline{T} \\ q_{111|1} + (1 - \frac{\pi_{1010}}{\pi_{1100}})\dot{T} & \text{if } \frac{q_{111|1}\pi_{1100}}{\pi_{1010}} \geq \overline{T} \\ q_{111|1} + (1 - \frac{\pi_{1010}}{\pi_{1100}})\ddot{T} & \text{if } \underline{T} < \frac{q_{111|1}\pi_{1100}}{\pi_{1010}} < \overline{T} \end{cases} \tag{79}$$

where
$$\dot{T} = \begin{cases} \underline{T} & \text{if } \pi_{1010} \leq \pi_{1100} \\ \overline{T} & \text{if } \pi_{1010} > \pi_{1100} \end{cases}$$

$$\ddot{T} = \begin{cases} \underline{T} & \text{if } \pi_{1010} \leq \pi_{1100} \\ \frac{q_{111|1}\pi_{1100}}{\pi_{1010}} & \text{if } \pi_{1010} > \pi_{1100} \end{cases}$$

Thus, given a fixed value of π_{1100}, the bounds for the SACE are given by:

$$\min(SACE \mid \pi_{1100}) = \frac{\min((\pi_{1111}\mathrm{E}(Y_i(1)\mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1)\mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1)\mid 1100))\mid \pi_{1100}) - (q_{111|0} + q_{110|0})}{\pi_{1111} + \pi_{1110} + \pi_{1100}}$$

$$\max(SACE \mid \pi_{1100}) = \frac{\max((\pi_{1111}\mathrm{E}(Y_i(1)\mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1)\mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1)\mid 1100))\mid \pi_{1100}) - (q_{111|0} + q_{110|0})}{\pi_{1111} + \pi_{1110} + \pi_{1100}}$$

From section 3.1, we know that π_{1100} is not point identified, but bounded: $\pi_{1100} \in I$, $I = [\max\{0, p_{11|0} + p_{10|0} - p_{10|1}\}, \ \min\{p_{10|0}, p_{10|1}\}]$, we have,

$$\min SACE = \min_{\pi_{1100} \in I} \left[\frac{\min((\pi_{1111}\mathrm{E}(Y_i(1) \mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1) \mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1) \mid 1100)) \mid \pi_{1100}) - (q_{111|0} + q_{110|0})}{\pi_{1111} + \pi_{1110} + \pi_{1100}} \right]$$

$$\max SACE = \max_{\pi_{1100} \in I} \left[\frac{\max((\pi_{1111}\mathrm{E}(Y_i(1) \mid 1111) + \pi_{1110}\mathrm{E}(Y_i(1) \mid 1110) + \pi_{1100}\mathrm{E}(Y_i(1) \mid 1100)) \mid \pi_{1100}) - (q_{111|0} + q_{110|0})}{\pi_{1111} + \pi_{1110} + \pi_{1100}} \right]$$

One can prove that the expression on the left side of equation (79) is continuous as a function of π_{1100} and both the functions on the left side of equations (78) and (79) are non-decreasing as functions of π_{1100}. Thus, the $\max SACE$ could be achieved when π_{1100} is $\min\{p_{10|0}, p_{10|1}\}$ which is the right end point of the range for π_{1100}, and the $\min SACE$ could be achieved when π_{1100} is $\max\{0, p_{11|0} + p_{10|0} - p_{10|1}\}$ which is the left end point of the range for π_{1100}. Based on this observation, we can obtain the formula for the bound of SACE which is given in (26) and (27).

B. The ARDSNet data

861 patients were randomized to receive mechanical ventilation with either lower tidal volume or traditional tidal volume. The lower tidal volume group contained 432 patients and the traditional tidal volume group contained 429 patients. We created our variables based on the recorded answers for the study termination form and weaning form.

The first time point (day 28) survival information is obtained through the "ST2DT" variable in the study termination sub-dataset which recorded the date of death. If the date of death for subject i is below day 28, then S_{1i} is 0 and the QOL is not defined; otherwise, S_{1i} is 1.

For the patients who survive to day 28, the QOL that whether patient was able to breathe without assistance by day 28 was well defined. The variable "UNASSIST" in the study termination sub-dataset recorded whether the patient was able to sustain unassisted breathing for ≥ 48 hours during the first 28 days after initiation of study

procedures. However, even if the patient sustained unassisted breathing for at least 48 hours, the patient could return to assisted breathing before day 28. The variable "ASSIST" recorded this information. If the patient returned to assisted breathing from unassisted breathing for at least 48 hours, the "ASSIST" was recorded as "Yes". Thus, for patients whose "UNASSIST" was recorded as "No", we view them as the ones who were not able to breathe without assistance by day 28. For patients whose "UNASSIST" was recorded as "Yes", and "ASSIST" was recorded as "No", we view them as the ones who were able to breathe without assistance by day 28; for patients whose "UNASSIST" was recorded as "Yes" and "ASSIST" was recorded as "Yes", each patient could either (a) have had unassisted breathing at some point and then returned to assisted breathing and still be on assisted breathing at day 28 or (b) have had unassisted breathing before day 28, returned to assisted breathing before day 28 and then returned to unassisted breathing before day 28. For these patients, we further use the weaning sub-dataset which recorded in detail about each patients' breathing status to figure out whether the patient was able to breathe without assistance by day 28.

Our second time point survival indicator is whether the patient was eventually discharged home with unassisted breathing. This information was recorded in the variable "STATUS" which described patient status at study termination.

References

Abadie A. (2002). Bootstrap tests for distributional treatment effects in instrumental variable models. *Journal of the American Statistical Association*, 97, 284-292.

Angrist, J. D. (1990). Lifetime Earnings and the Vietnam Era Draft Lottery: Evidence from Social Security Administrative Records. *American Economic Review*, 80, 3, pp. 313-336.

Angrist, J. D., Imbens, G. W., and Rubin, D. B. (1996). Identification of causal effects

using instrumental variables. *Journal of the American Statistical Association*, 91, pp. 444-455.

Angrist, J.D. and Krueger, A. B. (1991). Does Compulsory School Attendance Affect Schooling and Earnings? *Quarterly Journal of Economics*, 106,4, pp. 979-1014.

Beran, R. (1988). Balanced simultaneous confidence sets. *Journal of the American Statistical Association*, 83, pp. 679-697.

Brookhart, M. and Schneeweiss, S. (2007). Preference-based instrumental variable methods for the estimation of treatmen effects: assessing validity and interpreting results. *International Journal of Biostatistics*, 3, 14.

Chiba, Y. (2012). The large sample bounds on the principal strata effect with application to a prostate cancer prevention trial. *The International Journal of Biostatistics*, Vol. 8: Iss. 1, Article 12.

Chiba, Y. and VanderWeele, T. J. (2011). A simple method for principal strata effects when the outcome has been truncated due to death. *American Journal of Epidemiology*, 173(7), pp. 745-751.

Cheng, J. (2009). Estimation and inference for the causal effect of receiving treatment on a multinomial outcome. *Biometrics*, 65, pp. 96-103.

Cheng, J. and Small, D. (2006). Bounds on causal effects in three-arm trials with noncompliance. *Journal of the Royal Statistical Society, Series B*, 69, pp. 79-99.

Clarke, P.S. and Windmeijer, F. (2012). Instrumental variable estimators for binary outcomes. *Journal of the American Statistical Association*, 107, pp. 1638-1652.

Cox, D. R., Fitzpatrick, R., Fletcher, A. E., Gore, S. M., Spiegelhalter, D. J., and Jones, D. R. (1992). Quality-of-life assessment: Can we keep it simple? *Journals of the Royal Statistical Society: Series A,* 155, pp. 353-393.

Egleston, B. L., Scharfstein, D. O., Freeman, E. E., and West, S. K. (2007). Causal inference for non-mortality outcomes in the presence of death. *Biostatistics*, 8, pp. 526-545.

Efron, B. and Tibshirani, R. (1998) The problem of regions. *Annals of Statistics*, 26, pp. 1687-1718.

Frangakis, C. E. and Rubin, D. B. (2002). Principal stratification in causal inference. *Biometrics*, 58, pp. 21-29.

Freiman, M. and Small, D. (2013). Large sample bounds on the survivor average causal effect when outcomes are censored by death. (Under review)

Gilbert, P. B., Bosch, R. J., and Hudgens, M. G. (2003). Sensitivity analysis for the assessment of causal vaccine effects on viral load in HIV vaccine trials. *Biometrics*, 59, pp. 531-541.

Hayden, D., Pauler, D. K., and Schoenfeld, D. (2005). An estimator for treatment comparisons among survivors in randomized trials. *Biometrics*, 61, pp. 305-310.

Hernan, M., Robins, J. (2006). Instruments for causal inference: an epidemiologist's dream? *Epidemiology*, 17, 360.

Horowitz, J. and Manski, C. (2000). Nonparametric analysis of randomized experiments with missing covariate and outcome data. *Journal of the American Statistical Association*, 95, pp. 77-84.

Hudgens, M. G., Hoering, A., and Self, S. G. (2003). On the analysis of viral load endpoints in HIV vaccine trials. *Statistics in Medicine* 22, pp. 2281-2298.

Imai, K. (2008). Sharp bounds on the causal effects in randomized experiments with "truncation-by-death". *Statistics & Probability Letters*, 78, pp. 144-149.

Kling, J. R. (1999). The Effect of Prison Sentence Length on the Subsequent Employment and Earnings of Criminal Defendants. *Princeton University, Woodrow Wilson School*, Discussion Paper 208.

Lee, K. G.(September 2013). Intraventricular hemorrhage of the newborn. MedlinePlus. http://www.nlm.nih.gov/medlineplus/ency/article/007301.htm

Mealli, F. and Pacini, B. (2012). Using secondary outcomes and covariates to sharpen inference in randomized experiments with noncompliance. *Journal of the American Statistical Association*, DOI:10.1080/01621459.2013.802238

Rubin, D. B. (2000). Comment on causal inference without counterfactuals. *Journal of the American Statistical Association*, 95, pp. 435-438.

Tan Z. (2006). Regression and weighting methods for causal inference using instrumental variables. *Journal of the American Statistical Association*, 101, pp. 1607-1618.

Zhang, J. L., and Rubin, D. B. (2003). Estimation of causal effects via principal stratification when some outcomes are truncated by "death". *Journal of Educational and Behavioral Statistics*, 28, pp. 353-368.