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Causal inference for non-mortality outcomes in the presence of death

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SUMMARY

Evaluation of the causal effect of a baseline exposure on a morbidity outcome at a fixed time point is often complicated when study participants die before morbidity outcomes are measured. In this setting, the causal effect is only well defined for the principal stratum of subjects who would live regardless of the exposure. Motivated by gerontologic researchers interested in understanding the causal effect of vision loss on emotional distress in a population with a high mortality rate, we investigate the effect among those who would live both with and without vision loss. Since this subpopulation is not readily identifiable from the data and vision loss is not randomized, we introduce a set of scientifically driven assumptions to identify the causal effect. Since these assumptions are not empirically verifiable, we embed our methodology within a sensitivity analysis framework. We apply our method using the first three rounds of survey data from the Salisbury Eye Evaluation, a population-based cohort study of older adults. We also present a simulation study that validates our method.

Keywords: Causal inference; Competing risk; Emotional distress; Sensitivity analysis; Vision loss.

1. INTRODUCTION

In studies of older individuals, researchers are often interested in evaluating the effect of exposure on morbidity as well as mortality outcomes. When analyzing morbidity outcomes, the competing risk of death must be taken into account. Any meaningful analysis must recognize that a participant's morbidity outcome at a specified point in time is not defined if he/she died before that time.

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An analysis which compares morbidity outcomes for study participants who are observed to live in exposed and nonexposed groups is problematic, since the survivors in the exposed group are not necessarily exchangeable with the survivors in the nonexposed group. Further, participants who would live when they have the exposure might not live when they do not have the exposure, in which case even a poor morbidity outcome with exposure might be better than the mortality outcome without exposure.

There are numerous examples in the gerontologic literature in which researchers are interested in comparing non-mortality outcomes across treatment or exposure groups in panel surveys but find inferences complicated by the death of study participants between panels. Common approaches to this problem are to examine outcomes across observed survivors, considering those who died to be cases lost to follow-up, with occasional discussions about how inferences are affected by the fact that those who died differed from those who survived (Avlund *and others*, 2004; Gilley *and others*, 2004; van Hooren *and others*, 2005; Chen and Wilmoth, 2004; Steunenberg *and others*, 2005; Boerner *and others*, 2005). An alternative method, which changes the inferential objective, is to create a composite end point including death and morbidity (Avlund *and others*, 2004). The use of traditional survival analytic techniques that allows for the modeling of death as a competing risk are not necessarily applicable to these studies, since the time of death is often observed but the time of an incident morbidity outcome is not.

An additional limitation of traditional techniques is that they are generally not causally interpretable. When an exposure's effect on a non-mortality outcome is examined among the observed survivors at a fixed time point, it is not possible to disentangle the effect due to the exposure's impact on the non-mortality outcome from the exposure's impact on mortality among those at high risk of having the non-mortality outcome. If the propensity to have the non-mortality outcome is linked to the propensity to die, then it is possible that a harmful exposure will kill off a vulnerable population, leaving only healthy survivors. At the end of the study, the effect of the exposure might appear beneficial on the non-mortality outcome, when the effect is an artifact of the exposure's impact on mortality. The crux of the problem is that the non-mortality outcome is not defined if someone dies. It is not meaningful to compare a person's functional outcomes under two exposure categories if the person dies when they have one exposure but not the other. This limits the interpretability of effect estimates among study survivors. The growth of gerontologic analyses based on longitudinal panel surveys (Ferraro and Kelley-Moore, 2003) only heightens the need for interpretable estimands and inferential techniques for non-mortality outcomes.

Using the potential outcomes formalization of causal inference, developed by Neyman (1923), Rubin (1974), and Holland (1986), Frangakis and Rubin (2002) introduced a meaningful causal estimand: The causal effect of exposure on the morbidity outcome among participants who would live regardless of their exposure. Rubin (2000) and Hayden *and others* (2005) referred to this estimand as the survivors average causal effect (SACE). Robins (1995) proposed a conceptually similar estimand in the context of semi-competing risks, while Robins and Greenland (2000) described an estimand identical to SACE. SACE falls into a general class of estimands, called principal stratum causal effects, where a principal stratum is defined by potential outcomes (Frangakis and Rubin, 2002). In this context, the principal stratum is the set of participants who would survive regardless of their exposure.

The identification of SACE and other principal stratum causal effects usually rely on untestable assumptions. There has been a flurry of recent methodological work regarding inference about SACE and SACE-like estimands in the context of randomized studies. Table 1 compares and contrasts some of the key aspects of these works. Gilbert *and others* (2003) and Hudgens *and others* (2003) discussed inference about the causal effect of exposure among the participants who would become HIV infected regardless of whether they received a vaccine or placebo. While Hudgens *and others* (2003) focused on conditions for testing the null hypothesis of no causal effect, Gilbert *and others* (2003) discussed estimation under a class of identifiability conditions, indexed by an interpretable sensitivity analysis parameter. These authors assumed monotonicity, which states that "no subject would be infected if randomized to vaccine,

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Table 1. *Comparison of sensitivity analysis methods used for drawing inference about SACE or SACE-like estimands*

Gilbert *and others* (2003)	Randomized study, monotonicity, nonparametric estimation, bootstrap standard errors
Zhang and Rubin (2003)	Randomized study, population-level bounds
Hayden *and others* (2005)	Randomized study, assumptions conditioned on covariates, provides identification of the joint distribution of all the potential outcomes, maximum likelihood estimation, addresses missing non-mortality outcomes
Proposed method	Observational study, monotonicity, most assumptions conditioned on covariates, does not provide identification of the joint distribution of all the potential outcomes, estimating equations, large sample theory, addresses missing non-mortality outcomes

but would be uninfected if randomized to placebo." Zhang and Rubin (2003) discuss population bounds for SACE under no assumptions and under monotonicity, which in their context means that if a subject lives when given a placebo, he/she would also live when given a treatment. Hayden *and others* (2005) developed a likelihood-based sensitivity analysis procedure for estimating SACE. Their methodology incorporates covariates, does not impose monotonicity, and assumes a cumulative proportional odds model restriction. Their model admits identification of a joint distribution of the potential outcomes. They also address how their method can be adjusted to handle missing outcomes and, for this situation, propose using the bootstrap to obtain standard errors.

In this paper, we propose a sensitivity analysis procedure for drawing inference about SACE in the context of observational studies with missing outcomes among observed survivors. Our sensitivity analysis parameterization is similar to that of Gilbert *and others* (2003). While we impose monotonicity, our modeling approach does not yield identification of the entire joint distribution of potential outcomes, just features of the joint distribution which are necessary for estimating SACE. In contrast, Hayden *and others* (2005) seek identification of the entire joint distribution of the counterfactuals and as a consequence require more assumptions (even if monotonicity were imposed). The advantage of their approach is that it admits identification of other functionals of the joint distribution of the potential outcomes, although these functionals are not discussed in either the paper of Hayden *and others* or this paper.

The paper is organized as follows. In Section 2, we introduce our motivating observational study, the Salisbury Eye Evaluation (SEE), in which gerontologic researchers are interested in the effect of vision loss on emotional distress. In Section 3, we introduce the data structure and notation for the SEE study. In Section 4, we mathematically define SACE and present our two alternative sets of identifiability assumptions, indexed by sensitivity analysis parameters. We also discuss additional testable models for our estimation procedure. In Section 5, we introduce our estimators and derive their large sample properties. In Section 6, we apply SACE to the SEE study. We finish with a discussion in Section 7.

An R program to implement our method is available from the authors.

2. THE SEE

Visual impairment is a common problem in older adults, as 15–20% of adults in their 80s are afflicted (Munoz *and others*, 2000). Loss of vision can result in increased dependence on others, less social

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interaction, and increased disability. Therefore, these individuals may be at an increased risk of emotional distress, which may lead to further deterioration in health.

Some studies have found an association between visual impairment and the emotional distress symptom of depression, but to our knowledge almost all have been cross-sectional (Rovner *and others*, 1996; Scott *and others*, 2001; Rovner and Ganguli, 1998; Jorm *and others*, 1995; Carabellese *and others*, 1993). One problem with investigating this relationship longitudinally in older individuals is that death is a competing risk that is associated with both visual impairment and depression (McCarty *and others*, 2001; Klein *and others*, 1995; Thompson *and others*, 1989; Blazer *and others*, 2001; Schulz *and others*, 2000; Stern *and others*, 2001; Black and Markides, 1999).

To investigate if incident vision loss increases the risk of emotional problems, we used data from the SEE project, a population-based cohort study of older adults (West *and others*, 1997). In this study, visual acuity was assessed using the Early Treatment Diabetic Retinopathy Study eye chart, and emotional distress symptoms were assessed using the General Health Questionnaire (GHQ) which rates emotional distress on a scale of 0 to 28 (Goldberg and Hillier, 1979). Incident vision loss was defined as a loss of two or more lines on an eye chart of the best visual acuity possible with glasses at the second round, 2 years after the baseline round. Those with severe baseline visual impairment who were not able to have at least two lines of vision loss were excluded from the study. The outcome of interest was incident worsened emotional distress at the third round, which occurred 4 years later. Worsened emotional distress is defined by a worsening of four or more points in the total GHQ score. The total GHQ score has been found to have strong correlation with clinically relevant depression (Goldberg and Hillier, 1979).

Table 2 presents summary statistics of our sample. In the second and fourth columns of Table 2, we present summary statistics for each of these baseline characteristics, stratified by vision loss status. The third and fifth columns present summary statistics for the subgroup who survived past the third round, stratified by vision loss status. As shown in the table, a significant proportion of individuals died before emotional distress could be assessed at the last round (24.7% of those with vision loss versus 15.4% of those without vision loss). These high mortality rates underline the importance of accounting for death as a competing risk in these data.

In addition to death, loss to follow-up and worsening emotional distress symptom rates were higher for those with vision loss as compared to those without vision loss in our study. Within each vision loss stratum, the baseline characteristics for the entire stratum versus the subgroup who survived to round 3 and

Table 2. *Summary statistics for covariate and outcome data, stratified by vision loss status*

	No vision loss Round 2	No vision loss Survived past round 3	Vision loss Round 2	Vision loss Survived past round 3
N (% within group)	1998	1691 (84.6%)	162	122 (75.3%)
Survivors lost to follow-up		328 (19.4%)		33 (27.0%)
Worse emotional distress		142 (10.4%)		11 (12.4%)
Age* (SD)	75.02 (4.91)	74.67 (4.77)	76.23 (5.21)	75.88 (5.23)
Comorbidities* (SD)	2.71 (1.71)	2.60 (1.66)	3.06 (1.90)	2.90 (1.90)
Men (%)	40.9	39.2	48.1	46.7
White (%)	74.5	74.9	72.8	73.8
Diabetes (%)*	12.8	11.6	22.8	23.0
Hypertension (%)	41.0	40.5	48.1	46.7
Lowest quartile BMI (%)*	27.2	25.1	35.2	31.1
Ever smoked	59.7	57.7	67.3	64.8
<12 years education (%)	50.3	49.3	46.3	41.8

* $P < 0.05$ for comparisons of baseline characteristics (columns 2 and 4). SD, standard deviation.

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were not lost to follow-up were comparable. However, there were differences between vision loss strata. Those with vision loss tended to (a) be older, (b) have more comorbidities, (c) be more likely to be male, (d) be more likely to be nonwhite, (e) be more likely to have diabetes, (f) have lower body mass index (BMI), which is often clinically worse in older persons compared with a higher BMI, (g) smoke more, and (h) be better educated. Thus, those with vision loss tended to be less healthy. Not all these differences were statistically significant, however, as shown in Table 2. We designed our proposed estimator of SACE to correct for bias that could result from such loss to follow-up and baseline differences between those with and without vision loss in the data set.

For the analysis in Section 6, our reference population was drawn from the set of subjects who (a) survived through round 2; (b) had measures of visual acuity and emotional distress at round 2; (c) had information on covariates such as age, gender, race, diabetes, hypertension, number of comorbidities, BMI, smoking status, and education at round 2; and (d) had information on mortality through round 3. Missing measures of emotional distress among survivors at round 3 were due to loss to follow-up.

3. DATA STRUCTURE AND NOTATION

In the potential outcomes framework, it is assumed that, associated with each individual, there are outcomes under two states of nature: one when a person has vision loss and the other when the same person does not have vision loss. Only one of these states of nature is actually observed. Our data structure reflects this assumption.

Let $\mathbf{X}$ be the vector of covariates and let Z be an indicator of vision loss (1 if vision loss, 0 otherwise). Let $D(1)$ indicate a person's mortality outcome when they have vision loss (1 if death, 0 otherwise); similarly, define $D(0)$ to be the same person's mortality outcome when they do not have vision loss. Let $Y(1)$ be the emotional distress outcome when a person has vision loss and $Y(0)$ be the outcome when the same person does not have vision loss (1 if worsened emotional distress symptoms, 0 otherwise). $Y(0)$ and $Y(1)$ are only defined if a person survives with the respective vision loss.

Let $D = D(Z)$ and $Y = Y(Z)$ be the observed mortality and worsened distress outcomes. Let R be an indicator of whether a survivor is interviewed at the final survey round in our study (1 if not lost to follow-up, 0 otherwise). We assume that we observed n i.i.d. copies of the observed data,

$$\mathbf{O} = \{O_i = \{\mathbf{X}_i, Z_i, D_i, (R_i \text{ if } D_i = 0), \quad (Y_i \text{ if } D_i = 0 \text{ and } R_i = 1)\}, i = 1, \ldots, n\}.$$

Figure 1 is a graphical representation of the relationship between the observed and the potential data.

The goal is to use the observed data to draw inference about SACE, the odds ratio (OR) of worsening emotional distress in the group that would survive either with or without vision loss. Specifically, we define

$$\text{SACE} = \frac{\text{odds } P[Y(1) = 1 | D(0) = 0, D(1) = 0]}{\text{odds } P[Y(0) = 1 | D(0) = 0, D(1) = 0]}. \tag{3.1}$$

Note, however, that SACE could also have been defined as, say, a relative risk (RR) or risk difference.

In identifying SACE, we will find it useful to define the following quantities which are identifiable from the distribution of the observed data for $z = 0, 1$:

$$g_z(\mathbf{X}) = P[D = 0 | Z = z, \mathbf{X}],$$

$$h_z(\mathbf{X}) = P[Y = 1 | D = 0, Z = z, R = 1, \mathbf{X}].$$

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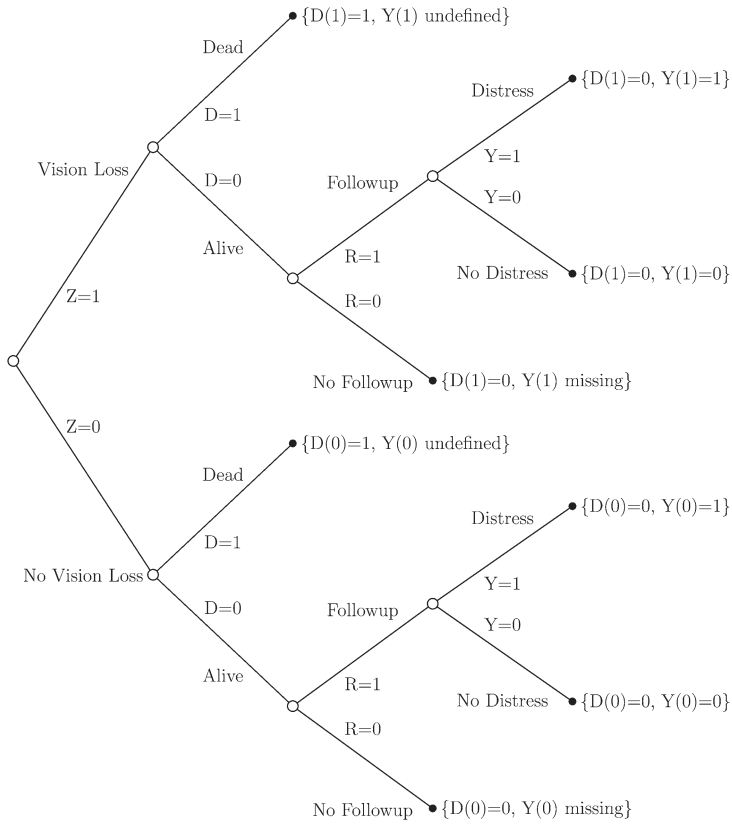

Fig. 1. Relation of observed to potential data.

4. Identification of SACE

In this section, we present assumptions to identify SACE from the observed data distribution. Before turning to these assumptions, we introduce an example, which will be used to demonstrate (a) the difficulty of drawing valid causal inferences from the observed data and (b) how the assumptions are used to identify SACE.

4.1 *Illustrative example*

Table 3 displays the potential outcomes and a binary covariate (X) for a hypothetical population of 4500 individuals. Within each level of X, the individuals are spread equally across the three principal strata: those who live regardless of their vision loss (S1) where $\{D(0) = 0, D(1) = 0\}$, those who would die if they had vision loss but survive if they did not (S2) where $\{D(0) = 0, D(1) = 1\}$, and those who would die both with and without vision loss (S3) where $\{D(0) = 1, D(1) = 1\}$. No individuals are in the stratum who would die without vision loss but survive with vision loss (S4) where $\{D(0) = 1, D(1) = 0\}$. Among the 1000 who would always be alive with $X = 0$, there is no emotional distress whatever be their vision loss. Among the 500 who would always be alive with $X = 1$, there is emotional distress whatever be their vision loss. For the individuals who would die only if they have vision loss, we see that their potential emotional distress outcomes when they have vision loss are not defined and two-thirds would have emotional distress when they do not have vision loss. For the individuals who die regardless of

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Table 3. *Potential outcome and covariate data for a hypothetical population*

No.	Principal stratum	X	$D(0)$	$D(1)$	$Y(0)$		$Y(1)$	
					0	1	0	1
1000	Always survivors (S1)	0	0	0	1000	0	1000	0
500	Always survivors (S1)	1	0	0	0	500	0	500
1000	Diers only with vision loss (S2)	0	0	1	0	1000	—	—
500	Diers only with vision loss (S2)	1	0	1	500	0	—	—
1000	Always diers (S3)	0	1	1	—	—	—	—
500	Always diers (S3)	1	1	1	—	—	—	—
0	Diers only with/without vision loss (S4)	0	1	0	—	—	0	0
0	Diers only with/without vision loss (S4)	1	1	0	—	—	0	0

their state of vision, their potential emotional distress outcomes are undefined. The causal effects among these latter strata are undefined. Causal inferences are only meaningful in the stratum of those who would always remain alive. In this stratum, the causal OR of emotional distress for vision loss versus no vision loss is 1 (i.e. no causal effect).

Only a coarse version of Table 3 is observable. In Table 4, we present the observed data. As in Table 3, there are 3000 subjects with $X = 0$ and 1500 with $X = 1$. Within levels of X, subjects are spread equally across the vision status stratum. Regardless of X, subjects who have vision loss have an odds of dying of two and subjects without vision loss have an odds of dying of 0.5. Among the survivors, half of the subjects have mental health assessments. For subjects who survive, and have mental health assessments, the OR of emotional distress between subjects with and without vision loss is 0.5. An incorrect interpretation of this analysis would suggest that, overall, vision loss is protective against emotional distress and the protection holds only for the subgroup with $X = 0$. Why do we see this result? For subjects who survive and have mental health assessments, the subgroup with no vision loss (see lines 1–4 of Table 4) is a mixture of those who would always remain alive and those who would die only if they had vision loss (half S1 and half S2), while the subgroup with vision loss (see lines 7–8 of Table 4) consists of subjects who would always remain alive (S1). Thus, these subgroups are not comparable with regard to their principal strata. Since the rate of emotional distress in S2 is higher than that in S1 as illustrated in Table 3, we see why vision loss "looks" protective.

4.2 *Assumptions*

We introduce the following non-identifiable assumptions in order to identify SACE from the distribution of the observed data. To identify SACE, we can separately identify (a) $P[Y(1) = 1|S1]$ and (b) $P[Y(0) = 1|S1]$. We make the common Stable Unit Treatment Value Assumption (Rubin, 1980) which states that an individual's potential outcomes are unrelated to both the vision loss status of other study participants and the mechanism by which the individual lost their vision. Below, we list the assumptions specific to our estimator and label them using terminology common to the field of causal inference where appropriate (Rosenbaum and Rubin, 1983).

Assumption 1. $D(0) \leqslant D(1)$ (Monotonicity).

Assumption 1 states that the development of vision loss does not improve the mortality outcome of an individual. This assumption is similar to assumptions made by Gilbert *and others* (2003) and Zhang and Rubin (2003). One might challenge this assumption if vision loss reduces mortality by restricting activities (e.g. walking) that might cause death in older adults (e.g. falls). In our analysis, we believe that such a

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Table 4. *Observed data for a hypothetical population*

Line	No.	X	Z	D	R	Y	No assumptions	Assumption 1	Truth
1	250	0	0	0	1	0	S1 or S2	S1 or S2	S1
2	250	0	0	0	1	1	S1 or S2	S1 or S2	S2
3	125	1	0	0	1	0	S1 or S2	S1 or S2	S1
4	125	1	0	0	1	1	S1 or S2	S1 or S2	S2
5	500	0	0	0	0	?	S1 or S2	S1 or S2	250 S1 and 250 S2
6	250	1	0	0	0	?	S1 or S2	S1 or S2	125 S1 and 125 S2
7	250	0	1	0	1	0	S1 or S4	S1	S1
8	125	1	1	0	1	1	S1 or S4	S1	S1
9	250	0	1	0	0	?	S1 or S4	S1	S1
10	125	1	1	0	0	?	S1 or S4	S1	S1
11	500	0	0	1	—	—	S3 or S4	S3	S3
12	250	1	0	1	—	—	S3 or S4	S3	S3
13	1000	0	1	1	—	—	S2 or S3	S2 or S3	500 S2 and 500 S3
14	500	1	1	1	—	—	S2 or S3	S2 or S3	250 S2 and 250 S3

protective effect of vision loss is at most negligible since visual impairment and vision loss have been shown to have a strong relationship with mortality (see Freeman *and others*, 2005, for a review). For the illustrative example, this assumption implies that no subjects are in the principal stratum of subjects who die only without vision loss (S4). In column 9 of Table 4, the stratum S4 is removed. Thus, for subjects in lines 7–12, we know their principal stratum.

Assumption 2. $Z \perp P|\mathbf{X}$ (Strong ignorability).

Assumption 2 states that the development of vision loss is unrelated to the potential outcomes given the covariates. Rosenbaum and Rubin (1983) referred to this assumption as "strong ignorability of treatment assignment." Since vision loss is not randomized, we assume that within strata of confounders there are no unmeasured differences between those who lose vision and those who do not. One implication of this assumption is that $P[D(z) = 0|\mathbf{X}] = g_z(\mathbf{X})$ and $P[Y(z) = 1|D(z) = 0, \mathbf{X}] = P[Y = 1|D = 0, Z = z, \mathbf{X}]$. Assumptions 1 and 2 imply that $E[g_0(\mathbf{X})] \geqslant E[g_1(\mathbf{X})]$.

In the illustration, where $\mathbf{X}$ is a one-dimensional binary variable, $g_0(0) = 2/3$, $g_0(1) = 2/3$, $g_1(0) = 1/3$, and $g_1(1) = 1/3$.

Assumption 3. $R \perp Y|D = 0, Z, \mathbf{X}$.

This assumption states that, for survivors, missingness of the morbidity outcome is independent of the value of the outcome within levels of exposure and covariates. This is related to the "missing at random" assumption of Rubin (1976). It allows one to identify the probability of emotional distress in the group of survivors with missing emotional distress outcomes, within levels of Z and $\mathbf{X}$. Together with Assumption 2, we have that $P[Y(z) = 1|D(z) = 0, \mathbf{X}] = h_z(\mathbf{X})$.

In our illustrative example, $h_0(0) = 0.5$, $h_0(1) = 0.5$, $h_1(0) = 0$, and $h_1(1) = 1$. Further, we can compute some key quantities that will be needed in the identification of SACE. In particular, $E[g_0(X)] = \frac{2}{3}$, $E[g_1(X)] = \frac{1}{3}$, $E[h_0(X)g_0(X)] = \frac{1}{3}$, and $E[h_1(X)g_1(X)] = \frac{1}{9}$. Here, we show how these assumptions can be used to identify SACE.

Under Assumptions 1–3,

$$P[Y(1) = 1|S1] = \frac{E[h_1(\mathbf{X})g_1(\mathbf{X})]}{E[g_1(\mathbf{X})]}. \tag{4.1}$$

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To see this, note that

$$P[Y(1) = 1|S1] = P[Y(1) = 1|D(1) = 0]$$
$$= \frac{E[P[Y(1) = 1|D(1) = 0, \mathbf{X}]P[D(1) = 0|\mathbf{X}]]}{E[P[D(1) = 0|\mathbf{X}]]}$$
$$= \frac{E[h_1(\mathbf{X})g_1(\mathbf{X})]}{E[g_1(\mathbf{X}]}.$$

The first equality follows from Assumption 1. The second equality follows from the properties of conditional and unconditional expectations. The third equality follows from Assumptions 2 and 3 and from the definition of $h_1(\mathbf{X})$ and $g_1(\mathbf{X})$.

Application of this formula to our illustration yields $P[Y(1) = 1|S1] = \frac{1}{9}/\frac{1}{3} = \frac{1}{3}$.

Assumption 4 contains two sub-assumptions, each of which can be used in the identification of $P[Y(0) = 1|S1]$. These are motivated by the following key identity:

$$P[Y(0) = 1|D(0) = 0] = P[Y(0) = 1|S1]P[D(1) = 0|D(0) = 0]$$
$$+P[Y(0) = 1|S2]\{1 - P[D(1) = 0|D(0) = 0]\}. \quad (4.2)$$

Such mixing equations are commonly used to identify causal estimands using observed data (Gilbert *and others*, 2003; Zhang and Rubin, 2003). Under Assumptions 1–3, the left-hand side of (4.2) is identifiable since

$$P[Y(0) = 1|D(0) = 0] = \frac{E[h_0(\mathbf{X})g_0(\mathbf{X})]}{E[g_0(\mathbf{X}]} \quad (4.3)$$

and the "mixing" probability $P[D(1) = 0|D(0) = 0]$ is identifiable since

$$P[D(1) = 0|D(0) = 0] = \frac{P[D(1) = 0]}{P[D(0) = 0]} = \frac{E[g_1(\mathbf{X})]}{E[g_0(\mathbf{X})]}. \quad (4.4)$$

These equalities can be proved using similar manipulations as in the proof of (4.1).

By specifying how $P[Y(0) = 1|S2]$ relates to $P[Y(0) = 1|S1]$ in (4.2), we can then solve (4.2) for $P[Y(0) = 1|S1]$.

Assumption 4a.

$$\frac{P[Y(0) = 1|S2]}{P[Y(0) = 1|S1]} = \tau_{\mathrm{RR}}, \quad (4.5)$$

where τ_{RR} is a specified constant, interpreted as the RR of worsening emotional distress without vision loss when comparing the group of individuals that would survive without vision loss but die with vision loss (S2) to the group of individuals who would live regardless of vision loss (S1). The constant τ_{RR} is non-identifiable from the observed data because we do not know to which principal stratum individuals who are observed in our study to survive without vision loss belong. To identify the principal strata directly, we would need to observe the counterfactual mortality outcomes that individuals would have had if they had vision loss for those in the study who did not actually develop vision loss. Since we do not observe those counterfactual outcomes, we need this assumption. Our final inferences about SACE will be displayed in the form of a sensitivity analysis. That is, SACE will be estimated over a range of τ_{RR} considered plausible by subject matter experts.

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Gilbert *and others* (2003) posed a similar assumption, while Hayden *and others* (2005) made one based on covariates. From a sensitivity analysis perspective, this modeling decision is critical. If we did condition on covariates and the covariates were high-dimensional, subject matter experts might find it unreasonable to assume a constant RR across all levels of $\mathbf{X}$. If τ_{RR} were chosen to depend on $\mathbf{X}$, then the sensitivity analysis would become too complicated to display. Under the conceptualization of the problem of Hayden *and others* (2005), we would need many more τ-like parameters, even with our monotonicity assumption, to identify our estimand, particularly when dealing with continuous outcomes. Hayden *and others* (2005) reduce the dimension of the sensitivity parameters in their work by assuming proportionality across all levels of $\mathbf{X}$.

A possible drawback to our approach is that there may be no immediate "anchoring point" of τ_{RR} which is considered plausible by scientific experts. For example, $\tau_{\mathrm{RR}} = 1$, which implies $Y(0)$ is independent of $D(1)$ given $D(0) = 0$, may be considered implausible. Instead, experts might be more comfortable anchoring the sensitivity analysis at an assumption that states that $Y(0)$ is independent of $D(1)$ given $D(0) = 0$ and $\mathbf{X}$. This assumption is part of what Hayden *and others* (2005) call "explainable nonrandom survival." We refer to it as "counterfactual conditional independence" (CCI) to emphasize that it is a conditional independence assumption involving two variables that we could never observe on the same person ($Y(0)$ is only observed if a person does not have vision loss, while $D(1)$ is only observed if a person does have vision loss). In our framework, $\tau_{\mathrm{RR}} = 1$ is simply "counterfactual independence," where we do not condition on any covariates to obtain independence. One can identify the unconditional τ_{RR} which corresponds to CCI. Then, an expert can use this value of τ_{RR} as their anchoring point in the sensitivity analysis. While anchoring might be a useful guide for scientific experts who desire a unique point estimate around which to base the sensitivity analysis, it is not essential. A sensitivity analysis can be performed over any range of τ_{RR} that is plausible, and this range of estimates can be reported. If the anchoring point is not within the sensitivity range, then researchers will have to reconsider whether the anchoring point assumption is scientifically meaningful or whether the range of τ_{RR} needs to be expanded.

Under Assumptions 1–3 and 4a,

$$P[Y(0) = 1|S1] = \frac{E[h_0(\mathbf{X})g_0(\mathbf{X})]}{E[g_1(\mathbf{X})] + \tau_{\mathrm{RR}}E[g_0(\mathbf{X}) - g_1(\mathbf{X})]}, \tag{4.6}$$

provided

$$\tau_{\mathrm{RR}} \geqslant \max\left\{0, \frac{E[h_0(\mathbf{X})g_0(\mathbf{X})] - E[g_1(\mathbf{X})]}{E[g_0(\mathbf{X})] - E[g_1(\mathbf{X})]}\right\} = \tau^{\dagger}_{\mathrm{RR}}. \tag{4.7}$$

When $E[g_0(\mathbf{X})] > E[g_1(\mathbf{X})]$, $P[Y(0) = 1|S1]$ decreases to 0 as $\tau_{\mathrm{RR}} \to \infty$. When $E[g_0(\mathbf{X})] = E[g_1(\mathbf{X})]$, $P[Y(0) = 1|S1] = E[h_0(\mathbf{X})g_0(\mathbf{X})]/E[g_1(\mathbf{X})]$, for all τ_{RR}.

Equation (4.6) is derived by plugging (4.3) and (4.4) into (4.2), substituting $\tau_{\mathrm{RR}}P[Y(0) = 1|S1]$ for $P[Y(0) = 1|S2]$, and solving for the unknown of interest, $P[Y(0) = 1|S1]$. The constraint in (4.7) is imposed to guarantee that the solution is a proper probability.

Using (4.1) and (4.6), we can compute SACE as a function of τ_{RR}. We denote this function as $\mathrm{SACE}_{\tau_{\mathrm{RR}}}(\cdot)$. This function, defined for τ_{RR} satisfying constraint (4.7), can be shown to be increasing in τ_{RR} when $E[g_0(\mathbf{X})] > E[g_1(\mathbf{X})]$.

In our illustration, the unknowable value of τ_{RR} is 2. Using this value, we see that $P[Y(0) = 1|S1] = \frac{1}{3}$. The bound in (4.7) equals $(\frac{1}{3} - \frac{1}{3})/(\frac{2}{3} - \frac{1}{3}) = 0$. Above, we saw that $P[Y(1) = 1|S1] = 1/3$. So, $\mathrm{SACE}_{\tau_{\mathrm{RR}}}(2) = 1$, indicating correctly that there is no causal effect of vision loss on emotional distress for

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those who would always survive regardless of vision loss. Figure 2 displays the function $\text{SACE}_{\tau_{\text{RR}}}(\cdot)$ for $\tau_{\text{RR}} \geqslant 0$ for our illustration. It is interesting to note that the unconditional τ_{RR} that is obtained under CCI is 1, yielding incorrect inference.

Instead of modeling the relationship between $P[Y(0) = 1|S2]$ and $P[Y(0) = 1|S1]$ via RR, we can also model the OR.

Assumption 4b.

$$\frac{\text{odds } P[Y(0) = 1|S2]}{\text{odds } P[Y(0) = 1|S1]} = \tau_{\text{OR}}, \tag{4.8}$$

where τ_{OR} is a specified constant, interpreted in the same manner as τ_{OR} but on the OR scale.

Under Assumptions 1–3 and 4b,

$$P[Y(0) = 1|S1] = \frac{E[h_0(\mathbf{X})g_0(\mathbf{X})]}{E[g_0(\mathbf{X})]}$$

when $\tau_{\text{OR}} = 1$. When $\tau_{\text{OR}} \neq 1$,

$$P[Y(0) = 1|S1] = -\frac{b(\tau_{\text{OR}}) + \sqrt{(b(\tau_{\text{OR}}))^2 - 4a(\tau_{\text{OR}})c}}{2a(\tau_{\text{OR}})}, \tag{4.9}$$

where

$$a(\tau_{\text{OR}}) = (1 - \tau_{\text{OR}})E[g_1(\mathbf{X})],$$

$$b(\tau_{\text{OR}}) = (\tau_{\text{OR}} - 1)(E[h_0(\mathbf{X})g_0(\mathbf{X})] + E[g_1(\mathbf{X})]) - \tau_{\text{OR}}E[g_0(\mathbf{X})],$$

$$c = E[h_0(\mathbf{X})g_0(\mathbf{X})].$$

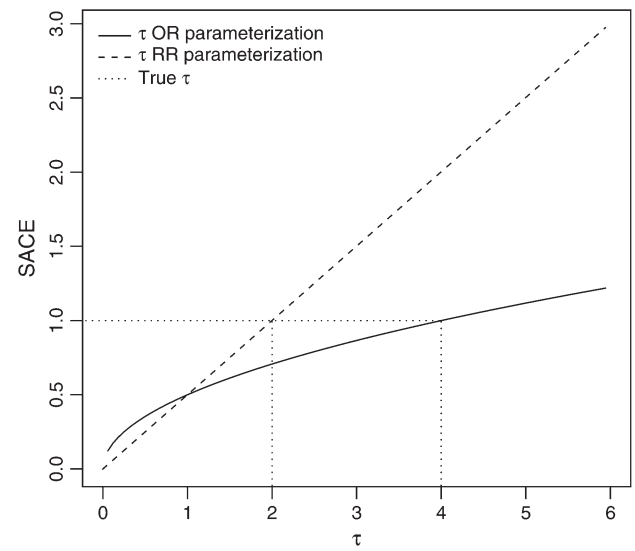

Fig. 2. SACE for illustrative data under RR & OR parameterizations of τ.

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As $\tau_{\mathrm{OR}} \to \infty$, $P[Y(0) = 1|S1]$ converges to

$$\frac{E[h_0(\mathbf{X})g_0(\mathbf{X})] + E[g_1(\mathbf{X})] - E[g_0(\mathbf{X})] + |E[h_0(\mathbf{X})g_0(\mathbf{X})] + E[g_1(\mathbf{X})] - E[g_0(\mathbf{X})]|}{2E[g_1(\mathbf{X})]}.$$

This result is derived by plugging (4.3) and (4.4) into (4.2), substituting

$$\frac{P[Y(0) = 1|S1]\tau_{\mathrm{OR}}}{P[Y(0) = 1|S1]\tau_{\mathrm{OR}} + 1 - P[Y(0) = 1|S1]}$$

for $P[Y(0) = 1|S2]$, and solving for the unknown of interest, $P[Y(0) = 1|S1]$. The solution is trivial when $\tau_{\mathrm{OR}} = 1$. When $\tau_{\mathrm{OR}} \neq 1$, the solution is found by solving a quadratic equation, of which only the above solution is a proper probability. The solution is a decreasing function of τ_{OR}. There are no constraints on τ_{OR}. Using (4.1) and (4.9), we can compute SACE as a function of τ_{OR}. We denote this function as $\mathrm{SACE}_{\tau_{\mathrm{OR}}}(\cdot)$. This function can be shown to be increasing in τ_{OR}.

In the illustration, the true $\tau_{\mathrm{OR}} = 4$. In (4.9), $a(4) = (1-4) \times \frac{1}{3} = -1, b(4) = (4-1) \times (\frac{1}{3} + \frac{1}{3}) - 4 \times \frac{2}{3} = -\frac{2}{3}, c = \frac{1}{3}$. So, $P[Y(0) = 1|D(0) = 0, D(1) = 0] = (-\frac{2}{3} + \sqrt{\frac{4}{9} + \frac{4}{3}})/2 = \frac{1}{3}$ and $\mathrm{SACE}_{\tau_{\mathrm{OR}}}(4) = 1$. This correctly indicates that there is no causal effect of vision loss on emotional distress for those who would always survive. Figure 2 displays the function $\mathrm{SACE}_{\tau_{\mathrm{OR}}}(\cdot)$ for all $\tau_{\mathrm{OR}} \geqslant 0$. As above, the unconditional τ_{OR} that is obtained under CCI is also 1, leading to invalid inference.

Study specific assumption. $\tau_{\mathrm{RR}} \geqslant 1$ and $\tau_{\mathrm{OR}} \geqslant 1$.

This assumption encodes a plausible belief about the direction of the RR of emotional distress in a world in which no one has vision loss when comparing two principal strata. The direction implies that the risk in such a world of no vision loss would be larger among the group who would live without vision loss only (but would die if they had vision loss) than in the group who would live both with and without vision loss. This assumption seems reasonable in that the group that would die if they had vision loss is likely less healthy and more frail than the group that would survive if they had vision loss. However, those who see this belief as arbitrary could estimate effects over any range of appropriate sensitivity values. In our example, the true values of τ_{RR} and τ_{OR} are 2 and 4, respectively. In other studies, researchers might use scientific information to obtain different bounds on the sensitivity parameter.

4.3 *Models for $g_z(\mathbf{X})$ and $h_z(\mathbf{X})$*

In the identification formulas above, we see that $P[Y(z) = 1|S1]$ can be expressed as a function of $\nu_0^* = P[D(0) = 0] = E[g_0(\mathbf{X})]$, $\nu_1^* = P[D(1) = 0] = E[g_1(\mathbf{X})]$, $\xi_0^* = P[D(0) = 0, Y(0) = 1] = E[h_0(\mathbf{X})g_0(\mathbf{X})]$, and $\xi_1^* = P[D(1) = 0, Y(1) = 1] = E[h_1(\mathbf{X})g_1(\mathbf{X})]$. This implies that SACE is a function of these quantities (see (4.6) and (4.9)). Thus, we need to compute $g_z(\mathbf{X})$ and $h_z(\mathbf{X})$. When $\mathbf{X}$ is high-dimensional, it is not possible to estimate these quantities non-parametrically, due to the curse of dimensionality. To achieve an estimator of SACE which converges at $\sqrt{n}$ rates, we will need to impose some lower-dimensional restrictions on these quantities. Specifically, we assume that, for $z = 0, 1$,

$$\mathrm{logit}\, g_z(\mathbf{X}) = g_z^\dagger(\mathbf{X}; \boldsymbol{\alpha}_z^*), \tag{4.10}$$

$$\mathrm{logit}\, h_z(\mathbf{X}) = h_z^\dagger(\mathbf{X}; \boldsymbol{\beta}_z^*), \tag{4.11}$$

where $g_z^\dagger(\mathbf{X}; \boldsymbol{\alpha}_z)$ and $h_z^\dagger(\mathbf{X}; \boldsymbol{\alpha}_z)$ are specified functions of $\mathbf{X}$ and parameter vectors $\boldsymbol{\alpha}_z$ ($j_z \times 1$) and $\boldsymbol{\beta}_z$ ($k_z \times 1$), respectively; $\boldsymbol{\alpha}_z^*$ and $\boldsymbol{\beta}_z^*$ denote the true parameter values. Under these models, we then

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see that

$$\nu_z^* = E[g_z(\mathbf{X})] = E[\text{expit}\{g_z^\dagger(\mathbf{X}; \boldsymbol{\alpha}_z^*)\}],$$

$$\xi_z^* = E[h_z(\mathbf{X})g_z(\mathbf{X})] = E[\text{expit}\{h_z^\dagger(\mathbf{X}; \boldsymbol{\beta}_z^*)\} \times \text{expit}\{g_z^\dagger(\mathbf{X}; \boldsymbol{\alpha}_z^*)\}],$$

where $\text{expit}\{x\} = \exp\{x\}/(1+\exp\{x\})$. Note that ν_z^* and ξ_z^* depend on $\boldsymbol{\alpha}_z^*$ and $\boldsymbol{\beta}_z^*$ as well as the distribution of $\mathbf{X}$.

5. ESTIMATION AND LARGE SAMPLE THEORY

Here we present the methods for estimating SACE. First, define

$$\boldsymbol{\psi}^* = (\boldsymbol{\alpha}_0^{*'}, \boldsymbol{\alpha}_1^{*'}, \boldsymbol{\beta}_0^{*'}, \boldsymbol{\beta}_1^{*'}, \nu_0^*, \nu_1^*, \xi_0^*, \xi_1^*)'.$$

We assume that $\boldsymbol{\psi}^* \in \boldsymbol{\Psi}$, where

$$\boldsymbol{\Psi} = \{\boldsymbol{\psi} = (\boldsymbol{\alpha}_0', \boldsymbol{\alpha}_1', \boldsymbol{\beta}_0', \boldsymbol{\beta}_1', \nu_0, \nu_1, \xi_0, \xi_1)' : \boldsymbol{\alpha}_z \in R^{j_z}, \boldsymbol{\beta}_z \in R^{k_z},$$

$$\nu_z \in (0,1), \xi_z \in (0,1), \nu_z > \xi_z, \nu_0 > \nu_1, z = 0, 1\}.$$

Under this notation and assumption, $\tau_{\text{RR}}^\dagger$ in (4.7) is equal to $\max\{0, \frac{\xi_0 - \nu_1}{\nu_0 - \nu_1}\} < 1$.

5.1 $\boldsymbol{\psi}^*$

To estimate $\boldsymbol{\psi}^*$, we first estimate $\boldsymbol{\alpha}_z^*$ and $\boldsymbol{\beta}_z^*$ via maximum likelihood using logistic regressions that include all the confounding covariates. We denote these estimators by $\widehat{\boldsymbol{\alpha}}_z$ and $\widehat{\boldsymbol{\beta}}_z$. Then, it is natural to estimate ν_z^* and ξ_z^* by

$$\widehat{\nu}_z = E_n[\text{expit}\{g_z^\dagger(\mathbf{X}; \widehat{\boldsymbol{\alpha}}_z)\}],$$

$$\widehat{\xi}_z = E_n[\text{expit}\{h_z^\dagger(\mathbf{X}; \widehat{\boldsymbol{\beta}}_z)\} \times \text{expit}\{g_z^\dagger(\mathbf{X}; \widehat{\boldsymbol{\alpha}}_z)\}],$$

where, for a random variable U on which we have n i.i.d. observations, $E_n[U] = \frac{1}{n}\sum_{i=1}^n U_i$. In words, we are using the results from the logistic regressions to estimate for each individual the probability of survival and the conditional probability of worsened emotional distress given survival for both potential vision loss categories. We then average the estimated survival probabilities within each vision loss category to obtain marginal estimated probabilities, $\widehat{\nu}_0$ and $\widehat{\nu}_1$. Similarly, we average the product of the estimated probabilities of survival and the estimated probabilities of worsened emotional distress given survival within each vision loss category to get estimated marginal probabilities of surviving with worsened emotional distress, $\widehat{\xi}_0$ and $\widehat{\xi}_1$. These estimators form the estimates needed for $\boldsymbol{\psi}^*$ which we call $\widehat{\boldsymbol{\psi}}$. Obtaining estimators in this way is equivalent to solving the following unbiased equation:

$$\sum_{i=1}^n \mathbf{U}(O_i; \boldsymbol{\psi}) = 0,$$

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where

$$\boldsymbol{U}(O;\boldsymbol{\psi}) = \big[\boldsymbol{U}_{\boldsymbol{\alpha}_0}(O;\boldsymbol{\psi})', \boldsymbol{U}_{\boldsymbol{\alpha}_1}(O;\boldsymbol{\psi})', \boldsymbol{U}_{\boldsymbol{\beta}_0}(O;\boldsymbol{\psi})', \boldsymbol{U}_{\boldsymbol{\beta}_1}(O;\boldsymbol{\psi})', U_{\nu_0}(O;\boldsymbol{\psi}),$$
$$U_{\nu_1}(O;\boldsymbol{\psi}), U_{\xi_0}(O;\boldsymbol{\psi}), U_{\xi_1}(O;\boldsymbol{\psi})\big]',$$

$$\boldsymbol{U}_{\boldsymbol{\alpha}_0}(O;\boldsymbol{\psi}) = \frac{\partial g_0^\dagger(\mathbf{X};\boldsymbol{\alpha}_0)}{\partial \boldsymbol{\alpha}_0}(1-Z)(1-D-\text{expit}\{g_0^\dagger(\mathbf{X};\boldsymbol{\alpha}_0)\}),$$

$$\boldsymbol{U}_{\boldsymbol{\alpha}_1}(O;\boldsymbol{\psi}) = \frac{\partial g_1^\dagger(\mathbf{X};\boldsymbol{\alpha}_1)}{\partial \boldsymbol{\alpha}_1} Z(1-D-\text{expit}\{g_1^\dagger(\mathbf{X};\boldsymbol{\alpha}_1)\}),$$

$$\boldsymbol{U}_{\boldsymbol{\beta}_0}(O;\boldsymbol{\psi}) = \frac{\partial h_0^\dagger(\mathbf{X};\boldsymbol{\beta}_0)}{\partial \boldsymbol{\beta}_0}(1-Z)R(1-D)(Y-\text{expit}\{h_0^\dagger(\mathbf{X};\boldsymbol{\beta}_0)\}),$$

$$\boldsymbol{U}_{\boldsymbol{\beta}_1}(O;\boldsymbol{\psi}) = \frac{\partial h_1^\dagger(\mathbf{X};\boldsymbol{\beta}_1)}{\partial \boldsymbol{\beta}_1} ZR(1-D)(Y-\text{expit}\{h_1^\dagger(\mathbf{X};\boldsymbol{\beta}_1)\}),$$

$$U_{\nu_0}(O;\boldsymbol{\psi}) = \text{expit}\{g_0^\dagger(\mathbf{X};\boldsymbol{\alpha}_0)\} - \nu_0,$$

$$U_{\nu_1}(O;\boldsymbol{\psi}) = \text{expit}\{g_1^\dagger(\mathbf{X};\boldsymbol{\alpha}_1)\} - \nu_1,$$

$$U_{\xi_0}(O;\boldsymbol{\psi}) = \text{expit}\{h_0^\dagger(\mathbf{X};\boldsymbol{\beta}_0)\}\text{expit}\{g_0^\dagger(\mathbf{X};\boldsymbol{\alpha}_0)\} - \xi_0,$$

$$U_{\xi_1}(O;\boldsymbol{\psi}) = \text{expit}\{h_1^\dagger(\mathbf{X};\boldsymbol{\beta}_1)\}\text{expit}\{g_1^\dagger(\mathbf{X};\boldsymbol{\alpha}_1)\} - \xi_1.$$

It is easy to show that $E[\boldsymbol{U}(O;\boldsymbol{\psi}^*)] = 0$. By the theory of M-estimation (Huber, 1964), it can be shown that, for $\boldsymbol{\psi}^* \in \boldsymbol{\Psi}$,

$$\sqrt{n}(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}^*) \xrightarrow{D} \text{Normal}(0, \Sigma^*),$$

where

$$\Sigma^* = E\left[\frac{\partial \boldsymbol{U}(O;\Theta)}{\partial \boldsymbol{\psi}}\right]^{-1} E[\boldsymbol{U}(O;\boldsymbol{\psi})\boldsymbol{U}(O;\boldsymbol{\psi})']E\left[\frac{\partial \boldsymbol{U}(O;\boldsymbol{\psi})}{\partial \boldsymbol{\psi}}\right]^{-1'}.$$

The covariance matrix Σ^* can be estimated by

$$\widehat{\Sigma} = E_n\left[\frac{\partial \boldsymbol{U}(O;\Theta)}{\partial \boldsymbol{\psi}}\right]^{-1} E_n[\boldsymbol{U}(O;\boldsymbol{\psi})\boldsymbol{U}(O;\boldsymbol{\psi})']E_n\left[\frac{\partial \boldsymbol{U}(O;\boldsymbol{\psi})}{\partial \boldsymbol{\psi}}\right]^{-1'}.$$

5.2 SACE(·)

Under Assumptions 1–3, 4a, (4.10) and (4.11), SACE becomes,

$$\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}}) = \text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}};\boldsymbol{\psi}^*) = \frac{\xi_1^*}{\nu_1^* - \xi_1^*} \times \frac{\nu_1^* + \tau_{\text{RR}}(\nu_0^* - \nu_1^*) - \xi_0^*}{\xi_0^*}.$$

For fixed τ_{RR} satisfying $\tau_{\text{RR}} > 1$, this function is continuously differentiable for all $\boldsymbol{\psi}^* \in \boldsymbol{\Psi}$. We estimate $\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}})$ by $\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}}, \widehat{\boldsymbol{\psi}})$. The large sample theory for this estimator can be found by

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employing the delta method. Specifically,

$$\sqrt{n}\left\{\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}};\widehat{\boldsymbol{\psi}}) - \text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}};\boldsymbol{\psi}^*)\right\} \xrightarrow{D} N\left(0, \Gamma_{\tau_{\text{RR}}}(\tau_{\text{RR}};\boldsymbol{\psi}^*)\right),$$

where

$$\Gamma_{\tau_{\text{RR}}}(\tau_{\text{RR}};\boldsymbol{\psi}^*) = \nabla\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}},\boldsymbol{\psi}^*)'\,\Sigma\,\nabla\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}},\boldsymbol{\psi}^*)$$

and $\nabla\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}},\boldsymbol{\psi})$ is the gradient of $\text{SACE}_{\tau_{\text{RR}}}(\tau_{\text{RR}},\boldsymbol{\psi})$ with respect to $\boldsymbol{\psi}$. The variance–covariance matrix $\Gamma_{\tau_{\text{RR}}}(\tau_{\text{RR}};\boldsymbol{\psi}^*)$ is consistently estimated by $\Gamma_{\tau_{\text{RR}}}(\tau_{\text{RR}};\widehat{\boldsymbol{\psi}})$.

Under Assumptions 1–3, 4b, (4.10) and (4.11), SACE becomes

$$\begin{aligned}\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}}) &= \text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}};\boldsymbol{\psi}^*)\\ &= \frac{\xi_1^*}{\nu_1^*-\xi_1^*}\times\frac{(\tau_{\text{OR}}-1)(\xi_0^*-\nu_1^*)-\tau_{\text{OR}}\nu_0^*+q(\tau_{\text{OR}},\psi^*)}{(1-\tau_{\text{OR}})(\xi_0^*+\nu_1^*)+\tau_{\text{OR}}\nu_0^*-q(\tau_{\text{OR}},\psi^*)},\end{aligned}$$

where

$$q(\tau_{\text{OR}},\psi^*) = [\{(\tau_{\text{OR}}-1)(\xi_0^*+\nu_1^*)-\tau_{\text{OR}}\nu_0^*\}^2 - 4(1-\tau_{\text{OR}})\nu_1^*\xi_0^*]^{1/2}.$$

For fixed τ_{OR} satisfying $\tau_{\text{OR}} > 1$, this function is continuously differentiable for all $\boldsymbol{\psi}^* \in \boldsymbol{\Psi}$. We estimate $\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}})$ by $\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}},\widehat{\boldsymbol{\psi}})$. The large sample theory for this estimator can be found by employing the delta method as above. Specifically,

$$\sqrt{n}\left\{\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}};\widehat{\boldsymbol{\psi}}) - \text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}};\boldsymbol{\psi}^*)\right\} \xrightarrow{D} N\left(0, \Gamma_{\tau_{\text{OR}}}(\tau_{\text{OR}};\boldsymbol{\psi}^*)\right),$$

where

$$\Gamma_{\tau_{\text{OR}}}(\tau_{\text{OR}};\boldsymbol{\psi}^*) = \nabla\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}},\boldsymbol{\psi}^*)'\,\Sigma\,\nabla\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}},\boldsymbol{\psi}^*)$$

and $\nabla\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}},\boldsymbol{\psi})$ is the gradient of $\text{SACE}_{\tau_{\text{OR}}}(\tau_{\text{OR}},\boldsymbol{\psi})$ with respect to $\boldsymbol{\psi}$. The variance–covariance matrix $\Gamma_{\tau_{\text{OR}}}(\tau_{\text{OR}};\boldsymbol{\psi}^*)$ is consistently estimated by $\Gamma_{\tau_{\text{OR}}}(\tau_{\text{OR}};\widehat{\boldsymbol{\psi}})$.

To guarantee that Wald-type confidence intervals for SACE are nonnegative, we recommend that the confidence interval first be computed for log(SACE) and then exponentiated. The asymptotic distribution of log(SACE) is found by the delta method.

We conducted a simulation study to evaluate the finite sample behavior of our estimation procedure for SACE, the results of which are presented in the supplementary material available at *Biostatistics* online (http://www.biostatistics.oxfordjournals.org). Overall, the results suggest that the inferences made using our asymptotic theory are generally valid. Misspecifying the correct sensitivity parameter, τ_{RR} or τ_{OR}, however, can lead to substantial bias. This underlines the importance of a sensitivity analysis approach to presenting results when the true τ_{RR} or τ_{OR} is unknown.

6. DATA ANALYSIS

We used data from the SEE study to demonstrate our method. Of the 2520 subjects in the study, 32 were not at risk of losing two lines of vision because of severe visual impairment, 137 died before their second round interview, and 191 had missing information or were lost to follow-up at or before the second round. These subjects were excluded. Of the remaining 2160 subjects, 162 had vision loss diagnosed at the second interview. In this data set, the covariates, **X**, are age, gender, race, diabetes, hypertension, number of comorbidities, BMI, smoking status, and education.

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We first used a naive logistic regression to investigate the effect of vision loss on emotional distress among the group observed to survive conditional on $\mathbf{X}$. After adjusting for covariates, subjects with vision loss have 1.26 times the odds of worsening emotional distress as compared to those without vision loss (95% CI: [0.65, 2.46]). The increase in the odds of distress is of modest clinical relevance and is not statistically different than 1 at the 0.05 Type-I error level.

Next, we employed our sensitivity analysis approach to estimate SACE. We fit models (4.10) and (4.11), in which the functions $g_z^\dagger(\mathbf{X};\boldsymbol{\alpha}_z)$ and $h_z^\dagger(\mathbf{X};\boldsymbol{\beta}_z)$ are assumed to be linear in age, sex, race, diabetic and hypertensive status, number of comorbidities, lowest quartile BMI, having ever smoked, and having a high school education.

Combining these results with Assumptions 1–3, we then estimated the key components needed to identify SACE. The estimate of $P[Y(1) = 1|D(1) = 0]$, the probability of emotional distress among survivors if everyone had been "assigned" vision loss, is 14.8% (95% CI: [8.6%, 24.2%]), higher than the (potentially) confounded estimate, from Table 2, of 12.4%. The estimate of $P[Y(0) = 1|D(0) = 0]$, the corresponding probability of emotional distress if everyone had been "assigned" no vision loss, is 10.6% (95% CI: [9.0%, 12.3%]), which is slightly higher than the (potentially) confounded estimate of 10.4%. The estimated conditional probability of surviving with vision loss given that one would also survive without vision loss, $P[D(1) = 0|D(0) = 0]$, is 93.5% (95% CI: [81.0%, 97.9%]). Plugging these estimates into (4.2) and assuming that $P[Y(0) = 1|S1] \leqslant P[Y(0) = 1|S2]$, we can see that the estimated values of $P[Y(0) = 1|S1]$ must lie between 0.044 and 0.106 and $P[Y(0) = 1|S2]$ must lie between 0.106 and 1. For fixed τ_{OR} between 1 and 15 (with associated τ_{RR} between 1 and 7.3), $P[Y(0) = 1|S1]$ decreases from 0.106 to 0.075 and $P[Y(0) = 1|S2]$ increases from 0.106 to 0.549. Hence, over this range of τ_{OR} and τ_{RR}, we are ranging over very broad discrepancies between $P[Y(0) = 1|S1]$ and $P[Y(0) = 1|S2]$.

Figure 3 presents the estimated values of SACE and associated confidence intervals over τ_{OR} ranging from 1 to 15 and τ_{RR} ranging from 1 to 7. We see that when the probability of emotional distress is the same regardless of whether an individual's potential outcomes indicate that an individual always lives or only lives without vision loss ($\tau_{\text{OR}} = \tau_{\text{RR}} = 1$), then the naive OR and SACE are similar. As τ_{OR} and τ_{RR} get larger, the probability of emotional distress given an individual always lives gets much smaller than the probability of emotional distress given that an individual only lives without vision loss. As a result, SACE gets larger. The slopes are very shallow because the estimated proportion of subjects in S2 is small. The unconditional τ_{RR} and τ_{OR} that correspond to CCI are both approximately 1.3 and 1.3, respectively. Under CCI, SACE = 1.50 (95% CI: [0.80, 2.82]).

7. Discussion

Our method of accounting for death as a competing risk provides a meaningful, readily interpretable, and easy to implement causal estimand. In our data analysis, we found that the point estimate of SACE was similar to that of the naive OR when there was no difference in the probability of worsening emotional distress symptoms between those who die only with vision loss versus those who never die whatever be their vision loss status. There were some changes in SACE over the specified range of τ_{OR} and τ_{RR}, but the results were only marginally significant. Further, the magnitude of the effect of vision loss on emotional distress seems modest in terms of clinical relevance except for large values of τ_{OR} or τ_{RR}.

SACE does not correct for bias of the naive OR; the two ORs are measuring different quantities. The naive OR measures the effect of vision loss on emotional distress among those who are observed to live. Under Assumption 1, some of those who we observed to survive without vision loss would have died with vision loss; our causal estimand excludes this group. For this reason, even when τ_{OR} or τ_{RR} equals 1, the interpretation of SACE and the naive OR are different and the point estimates can be expected to differ, as was the case in our analysis.

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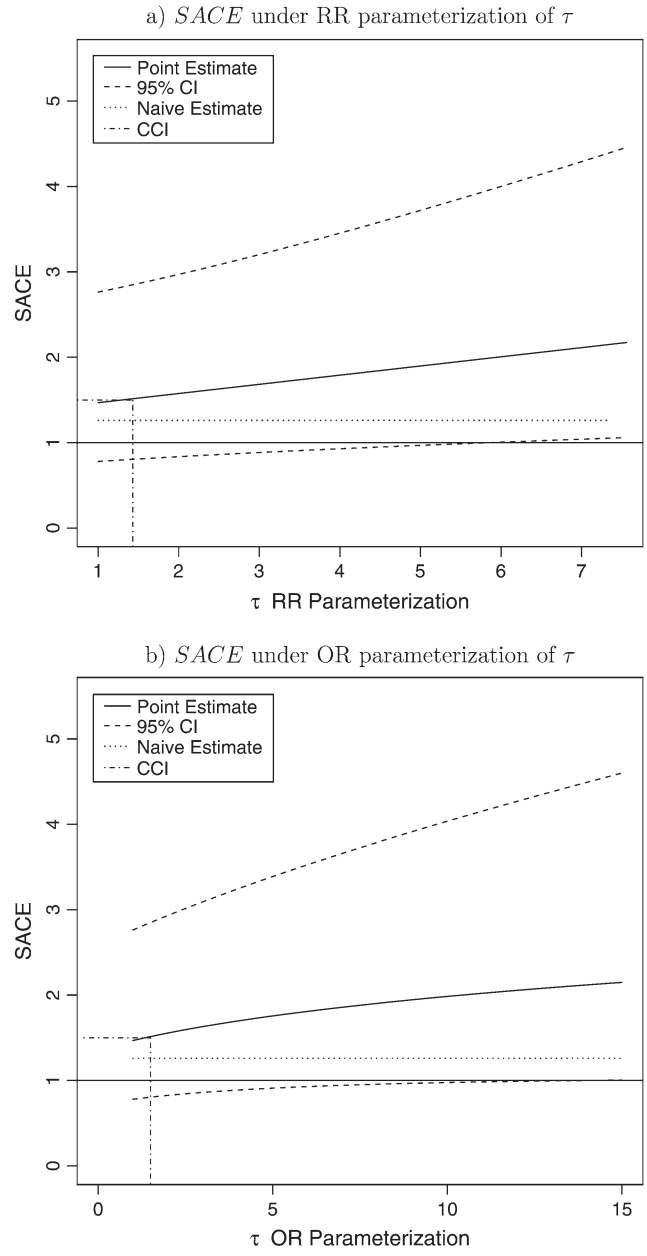

Fig. 3. Estimates of SACE. (a) SACE under RR parameterization of τ. (b) SACE under OR parameterization of τ.

Our method can be applied to continuous outcomes by replacing $P[Y(0) = 1|S1]$ and $P[Y(1) = 1|S1]$ with $E[Y(0)|S1]$ and $E[Y(1)|S1]$ and examining the difference in the expectations. A few changes are necessary for implementation in the continuous case. First, a model is needed for $h_z(\mathbf{X}) = E[Y|D = 0, Z = z, R = 1, \mathbf{X}]$ instead of the logit model specified above. While τ_{OR} is not applicable in the continuous case, one can still use $E[Y(0)|S2]/E[Y(0)|S1]$ in place of Assumption 4a for identification.

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If the continuous variable is bounded, a restriction similar to that presented in (4.7) is necessary to ensure that $E[Y(0)|S1]$ is within the appropriate bounds. One would also need to replace expit$\{h_z^\dagger(\mathbf{X}; \boldsymbol{\beta}_z)\}$ with $h_z^\dagger(\mathbf{X}; \boldsymbol{\beta}_z)$ in the estimating equations presented in Section 5.

One potential criticism of this work is that vision loss is not manipulable in the same manner as a randomized treatment. As Holland (1986) wrote, many have historically believed that Rubin's causal model is only applicable if one can conceptualize being able to manipulate the exposure. Under this conceptualization, immutable attributes such as sex are not considered causes. Changing the sex changes the person in too many ways to consider sex to be an underlying cause of anything. While vision loss may not be as manipulable as a randomized treatment, vision loss is an increasingly preventable and treatable condition; proper treatment can prevent vision loss due to glaucoma while laser-assisted *in situ* keratomileusis (LASIK) and cataract surgery can be used to reverse vision loss. As demonstrated by Freeman *and others* (2005), vision researchers are interested in causal effects of vision loss.

The methods described here should be of use to many researchers who examine outcomes when death is a strong competing risk in observational studies. We are confident that scientists will increasingly use estimators of SACE in their substantive work once they become more familiar with the concept of principal stratification, and once computer programs to estimate SACE are made more widely available.

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