

Truncation by death in the sufficient-cause framework

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Abstract

The sufficient-cause framework has been used for decades to improve our understanding of both basic and complex causal concepts in epidemiology, such as mediation and interaction. Here, we make use of this framework to provide a description of truncation by death, in which the outcome of interest is undefined for individuals who die before the assessment time at the end of follow-up. We explain the noncausal nature of the crude estimand that compares outcomes by treatment levels conditional on observed survival by showing that it corresponds to a comparison of distinct risk-status types, which are defined based on their susceptibility to sufficient causes. Further, expressions for the crude estimand and for the survivor average causal effect (SACE)—a causal estimand defined under the principal stratification approach—are provided in terms of population-level joint frequencies of the background factors of sufficient causes. Finally, we also describe conditions, based on background factors of sufficient causes, under which the SACE is null. Our description of this problem, which studies truncation by death from a new perspective, might encourage further analyses of principal stratification-based estimands using sufficient causes.

Key words causal mechanisms, potential outcomes, principal stratification, sufficient causes

Introduction

In epidemiologic studies where the outcome of interest is only defined for individuals who are alive at the end of the follow-up, when assessment occurs, if some participants die during the follow-up, the inferential problem of truncation by death might be present^{1,2} and can affect not only observational studies but also randomized clinical trials³ (see ICH E9(R1) Addendum⁴). In this situation, analyses that condition on observed survival do not represent a causal estimand, that is, a contrast of potential outcomes for the same set of units under different treatment levels.^{5,6} An approach that avoids this problem and that is often considered in this setting uses the principal stratification approach⁷ and involves defining a principal effect for the stratum of the population who would survive to the time of outcome assessment regardless of exposure or treatment level. Because it has a causal interpretation, this would be a suitable target estimand (note that Stensrud and colleagues⁸ recently proposed conditional separable effects as another suitable estimand).

Although the principal stratification approach, which is based on the more general potential outcomes framework for causal inference,^{5,9} has led to a rich literature on truncation by death, that includes discussions on identification, methods for estimation and sensitivity analyses of principal effects^{6,10–14}—a description

of truncation by death under other causal frameworks might be valuable.^{15–18} In particular, descriptions of causal processes under the sufficient-cause framework may be useful.¹⁹ This causal framework is based on the presence or absence of causal mechanisms, which are sufficient causes that once completed invariably lead to the outcome, and their components. This framework might not only provide information on the types of sufficient causes captured by different estimands used in the presence of truncation by death, but also lead to a more in-depth understanding of the potential biases in this context. Indeed, in many areas of epidemiologic research, the framing of questions using the sufficient-cause framework has led to a better characterization of key concepts.^{15–17,20–28}

In the following section, we briefly summarize the principal stratification approach for truncation by death. We then use the sufficient-cause framework to present this problem in the realistic scenario where a common cause of both survival and the outcome is present. It is important to clarify that our goal in providing an account of truncation by death using sufficient causes is not to describe new estimands, identification or estimation approaches for this problem; rather, our objective is to gain a better understanding of this problem by considering individual causal mechanisms and their relations to survival and the outcome of interest.

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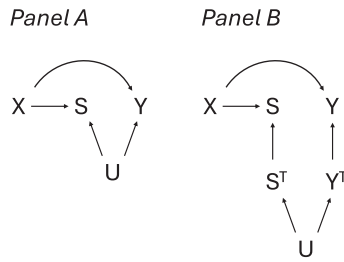


Figure 1 Directed acyclic graphs representing the truncation by death setting. Variables X , S , and Y denote treatment, survival, and the outcome of interest, respectively; variable U denotes common causes of survival and the outcome. (A) Note that conditioning on $S = 1$ likely induces collider bias, and that the relationship between X and U is symmetrical; both X and U are common causes of S and Y . (B) S^T and Y^T , response-type variables of S and Y , respectively, are also presented. Given that here we consider the SACE, which involves conditioning on $S^T = (1, 1)$, panel B is appropriate⁶.

Methods

The principal stratification approach to truncation by death

Consider a randomized trial recruiting patients with a serious medical condition in which the outcome, Y , corresponds to a dichotomized version of a quality of life score 1 year after trial enrolment (1 = quality of life score above a prespecified threshold, 0 = quality of life score below a prespecified threshold). The treatment is denoted by X (1 = patient is treated, 0 = patient is not treated); survival status 1 year after enrolment is indicated by the variable S (1 = patient is alive at the time of outcome assessment, 0 = patient died during the follow-up). An essential feature of the problem of truncation by death is that Y is undefined for individuals with $S = 0$. This setting is represented in the directed acyclic graph in Figure 1A, where the variable U denotes the common causes of survival and the outcome; here, for concreteness, we let U correspond to a binary variable that denotes age (1 = under 60 years, 0 = 60 years or above), which, we assume, affects both survival and quality of life. In studies affected by truncation by death, it is often assumed that factors that influence both survival and the outcome of interest are present.^{6,29}

To define a causal effect that is relevant in this context, we also use the potential outcome variables, S^x , which correspond to the survival status under treatment level x , and Y^x , the potential value of the outcome variable under treatment level x . In Figure 1B, response-type variables $S^T = (S^1, S^0)$ and $Y^T = (Y^1, Y^0)$, defined using potential outcomes, are presented.^{6,30} The S -related variable can be used to partition the study population into 4 principal strata: $(S^1, S^0) = (1, 1)$, $(S^1, S^0) = (1, 0)$, $(S^1, S^0) = (0, 1)$, $(S^1, S^0) = (0, 0)$. This principal stratification identifies a subgroup of the population for whom an effect of X on Y can be defined—the principal stratum of “always-survivors” $(S^1, S^0) = (1, 1)$; unlike in the other strata, Y^x is defined under both treatment levels for this stratum. Given the above, the following quantity, often referred to as the survivor average causal effect (SACE),^{11,13} would have a causal interpretation in settings where the outcome is truncated by death:

$$\text{SACE} \triangleq E[Y^1 - Y^0 | (S^1 = 1, S^0 = 1)].$$

Note that the target population of the SACE is the always-survivors, who are not discernible without strong assumptions, as only 1 of the

2 potential outcome variables S^1 and S^0 is observable for a particular individual. Furthermore, the SACE can also be defined for strata of the variable U , as shown below:

$$\text{SACE}_u \triangleq E[Y^1 - Y^0 | (S^1 = 1, S^0 = 1), U = u].$$

The SACE_u may vary across the values of U , which is referred to as effect modification of the SACE.¹⁰ When there is a common cause U of survival and the outcome, effect modification of the SACE may also occur by another variable that causes survival but does not affect the outcome.¹⁰ Note that the SACE is written as a weighted average of SACE_u , as shown below¹⁰:

$$\begin{aligned} \text{SACE} &\triangleq E[Y^1 - Y^0 | (S^1 = 1, S^0 = 1)] \\ &= \sum_u E[Y^1 - Y^0 | (S^1 = 1, S^0 = 1), U = u] \cdot P(U = u | (S^1 = 1, S^0 = 1)) \\ &= \sum_u \text{SACE}_u \frac{P((S^1 = 1, S^0 = 1), U = u)}{P((S^1 = 1, S^0 = 1))} \\ &= \sum_u \text{SACE}_u \frac{P((S^1 = 1, S^0 = 1), U = u)}{\sum_{u'} P((S^1 = 1, S^0 = 1), U = u')}. \end{aligned}$$

Results

Truncation by death in the sufficient-cause framework

In the sufficient-cause framework, using the definitions of X and S above, and explicitly considering U , we can enumerate 9 different types of sufficient causes for survival S as follows³¹: $A_1, A_2X, A_3\bar{X}, A_4U, A_5\bar{U}, A_6UX, A_7U\bar{X}, A_8\bar{U}X$, and $A_9\bar{U}\bar{X}$, where $\bar{X}$ and $\bar{U}$ denote the complements of X and U , respectively, in the terminology of events, and A_k ($k = 1, \dots, 9$) represents background factors necessary for the completion of the corresponding sufficient cause k . The sufficient causes can be interpreted as follows: sufficient cause A_1 will lead to survival regardless of the presence or absence of X and U ; sufficient cause A_2X implies that the presence of X will lead to survival whenever A_2 is present (regardless of the presence or absence of U); sufficient cause $A_3\bar{X}$ implies that the absence of X will lead to survival whenever A_3 is present (regardless of the presence or absence of U); sufficient causes A_4U and $A_5\bar{U}$ are analogous to A_2X and $A_3\bar{X}$, but, instead of X , are defined based on the presence and absence of U , respectively; finally, sufficient causes $A_6UX, A_7U\bar{X}, A_8\bar{U}X$ and $A_9\bar{U}\bar{X}$ require either the presence or absence of X and U .

Now, if we consider sufficient causes of the outcome “quality of life score above a prespecified threshold” ($Y = 1$), by the definition of truncation by death, they all require the presence of survival (ie, these sufficient causes require survival as a component cause). Thus, we can enumerate 9 different types of sufficient causes for the outcome Y as follows: $B_1S, B_2SX, B_3S\bar{X}, B_4SU, B_5S\bar{U}, B_6SUX, B_7SU\bar{X}, B_8\bar{S}UX$, and $B_9\bar{S}\bar{U}\bar{X}$, where B_k ($k = 1, \dots, 9$) represents background factors for sufficient cause k . Their interpretations are analogous to those in the previous paragraph. Note that we consider 2 stages of the causal process: the survival stage and the outcome stage; this is analogous to discussions on mediation based on the sufficient-cause framework,³² even though survival, in the context of truncation by death, is not a mediator (Figure 1A).

Here, for ease of discussion and visualization, we assume sufficient cause positive monotonicity for both X and U on S and Y (see Figure 2). Put differently, using the definitions of these variables in the previous

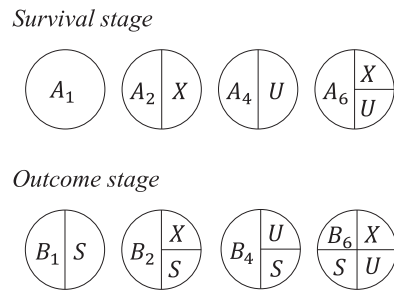


Figure 2 Sufficient causes in the context of truncation by death with a common cause of survival and the outcome. We consider 2 stages: the survival stage and the outcome stage. The exposure, the survival variable, and the common cause of survival and the outcome are represented by X , S , and U , respectively. We assume sufficient cause positive monotonicity for both X and U ; note that the relationship between X and U is symmetrical.

section, we assume that sufficient causes for survival (S) and for quality of life (Y) in which either the absence of treatment ($\bar{X}$) or an age of 60 years or above ($\bar{U}$) are component causes are not present in the population. Thus, only the following 4 types of sufficient causes for S might be present in the population: A_1 , A_2X , A_4U , and A_6UX . Similarly, only the following 4 types of sufficient causes for Y might be present in the population: B_1S , B_2SX , B_4SU , and B_6SUX . Consequently, a total of $256 (= 2^4 \times 2^4)$ risk-status types can be enumerated (Table S1), which are defined by possible combinations of susceptibility to sufficient causes.²¹ Note that, under the sufficient cause positive monotonicity assumption, the $SACE$ and $SACE_u$ are non-negative.

Some risk-status types only contribute to 1 of the 2 terms in $E[Y|S=1, X=1] - E[Y|S=1, X=0]$. Even for the corresponding quantities defined within strata of U , that is, $E[Y|S=1, X=1, U=u] - E[Y|S=1, X=0, U=u]$, a subset of the risk-status types only contributes to 1 of the terms. For instance, individuals of risk-status types 17 to 32 in Table S1 are susceptible only to A_6UX for survival. When $X=1$ and $U=1$ (in words, for the subgroup aged < 60 years who receive treatment), the sufficient cause A_6UX completes; these individuals, by definition, survive and contribute to data on quality of life, and consequently, of $E[Y|S=1, X=1, U=1]$. However, when $X=0$ and $U=1$ (individuals aged < 60 years who are not treated), no sufficient causes complete for survival; they do not survive, and their quality of life, the outcome Y , cannot be defined. Thus, they do not contribute to data of $E[Y|S=1, X=0, U=1]$.

As mentioned above, the target population of the $SACE$ is the always-survivors (ie, $(S^1, S^0) = (1, 1)$). Notably, membership to the always-survivors is a function of U for some individuals. In other words, an individual of particular risk-status types would be in the always-survivors stratum if her or his value of U were 1, but not if this value were 0. For example, let us consider individuals of risk-status type 33, who are susceptible only to A_4U for survival (Table S1). If they are younger than 60 years ($U=1$), the sufficient cause A_4U completes irrespective of the treatment and they are always-survivors. However, if they are 60 years or older ($U=0$), no sufficient causes complete irrespective of the treatment and they are “never-survivors” (ie, $(S^1, S^0) = (0, 0)$). In fact, under the sufficient cause positive monotonicity assumption, when $U=1$ holds, individuals who are susceptible to A_1 or A_4U for survival are always-

survivors, and there are $192 (= 3 \times 2^6)$ risk-status types (Table 1). By contrast, when $U=0$ holds, individuals who are susceptible to A_1 for survival are always-survivors, and there are $128 (= 2^7)$ risk-status types (Table 1). Therefore, individuals who are not susceptible to A_1 but are susceptible to A_4U are always-survivors if $U=1$, while they are not if $U=0$; they are either never-survivors (ie, $(S^1, S^0) = (0, 0)$) or survive only under treatment, which is referred to as “protectable” (ie, $(S^1, S^0) = (1, 0)$) (Table 1). In the upper part of Table 2, we provide expressions of $E[S|X=1]$, $E[S|X=0]$, $E[S|X=1] - E[S|X=0]$, and $\Pr(S^1=1, S^0=1)$ in terms of background factors A_k and U .

Conditions under which SACE is null

Recall that the $SACE$ can be expressed as a weighted average of $SACE_u$,¹⁰ and since $SACE_u \geq 0$ holds under the assumption of sufficient cause positive monotonicity, the $SACE$ is null if and only if $SACE_u$ is null for each level u . Therefore, we here describe conditions under which $SACE_u$ is null—in other words, conditions under which the treatment X has no effect on the outcome Y among the always-survivors with a particular value of U . Firstly, among those who are younger than 60 years ($U=1$), the $SACE_{u=1}$ is, by definition, null among those with $(A_1 \vee A_4) \wedge \{(B_1 \vee B_4) \vee (\bar{B}_2 \wedge \bar{B}_6)\}$, which is met by 156 of the 192 risk-status types that represent always-survivors under $U=1$ (ie, those individuals susceptible to A_1 or A_4U) (Table 1). Thus, the $SACE_{u=1}$ becomes null if and only if there are no individuals with $U=1$ for whom $(A_1 \vee A_4) \wedge \{(\bar{B}_1 \wedge \bar{B}_4) \wedge (B_2 \vee B_6)\}$ holds (ie, $\Pr((A_1 \vee A_4) \wedge \{(\bar{B}_1 \wedge \bar{B}_4) \wedge (B_2 \vee B_6)\} \wedge U) = 0$) (Figure 3). Note that, under this condition, protectable and never-survivors may be present among those with $U=1$. As an illustration, consider individuals younger than 60 years ($U=1$) of the risk-status type 35, who are susceptible only to A_4U for survival S and only to B_4SU for the outcome Y (Table S1). As mentioned above, they are always-survivors, and the sufficient cause B_4SU completes to induce the outcome Y irrespective of treatment (ie, $Y^1 = Y^0 = 1$); the effect of X on Y is null. By contrast, among those who are aged 60 years or older ($U=0$), the $SACE_{u=0}$ is null among those with $A_1 \wedge (B_1 \vee \bar{B}_2)$, which is met by 96 of the 128 risk-status types that represent always-survivors under $U=0$ (ie, those individuals susceptible to A_1) (Table 1). Thus, the $SACE_{u=0}$ becomes null if and only if there are no individuals with $U=0$ for whom $A_1 \wedge (\bar{B}_1 \wedge B_2)$ holds (ie, $\Pr(A_1 \wedge (\bar{B}_1 \wedge B_2) \wedge \bar{U}) = 0$) (Figure 3). Note that, under this condition, protectable and never-survivors may be present among those with $U=0$. For instance, let us consider individuals aged 60 years or older ($U=0$) of the risk-status type 137, who are susceptible only to A_1 for survival S and only to B_1S for the outcome Y (Table S1). They are always-survivors, and the sufficient cause B_1S completes irrespective of treatment (ie, $Y^1 = Y^0 = 1$); the effect of X on Y is null among them. To summarize, the conditions given for $SACE_u$, jointly, correspond to the condition for the $SACE$ to be null (ie, $\Pr((A_1 \vee A_4) \wedge \{(\bar{B}_1 \wedge \bar{B}_4) \wedge (B_2 \vee B_6)\} \wedge U) = 0$ and $\Pr(A_1 \wedge (\bar{B}_1 \wedge B_2) \wedge \bar{U}) = 0$) (Figure 3). In the middle part of Table 2, we provide expressions of some estimands including the $SACE$ in terms of background factors A_k and B_k as well as U .

Note, however, that even if the conditions described above for the $SACE_u$ is null hold, the crude estimand $E[Y|S=1, X=1, U=u] - E[Y|S=1, X=0, U=u]$ may not be null. First, let us consider individuals younger than 60 years ($U=1$). If $\Pr((A_1 \vee A_4) \wedge \{(\bar{B}_1 \wedge \bar{B}_4) \wedge (B_2 \vee B_6)\} \wedge U) = 0$ holds, which means $SACE_{u=1}$ is null, $E[Y|S=1,$

Table 1 Descriptions of always-survivors and their risk-status types.

Descriptions	Expressions in terms of background factors	The number of possible risk status types	Possible risk status types
Always-survivors if $U = 1^a$	$A_1 \vee A_4$	192 ($= 3 \times 2^6$)	33-64, 97-256
Always-survivors among whom $SACE_{U=1}$ is null	$(A_1 \vee A_4) \wedge \{(B_1 \vee B_4) \vee (\overline{B_2} \wedge \overline{B_6})\}$	156 ($= 3 \times 2^6 - 3^2 \times 2^2$)	33, 35, 36, 39-49, 51, 52, 55-64, 97, 99, 100, 103-113, 115, 116, 119-129, 131, 132, 135-145, 147, 148, 151-161, 163, 164, 167-177, 179, 180, 183-193, 195, 196, 199-209, 211, 212, 215-225, 227, 228, 231-241, 243, 244, 247-256
Always-survivors if $U = 0$	A_1	128 ($= 2^7$)	129-256
Always-survivors among whom $SACE_{U=0}$ is null	$A_1 \wedge (B_1 \vee \overline{B_2})$	96 ($= 3 \times 2^5$)	129-132, 137-148, 153-164, 169-180, 185-196, 201-212, 217-228, 233-244, 249-256
Always-survivors if $U = 1$ but not if $U = 0$	$\overline{A_1} \wedge A_4$	64 ($= 2^6$)	33-64, 97-128
Always-survivors if $U = 1$ but never-survivors if $U = 0$	$\overline{A_1} \wedge \overline{A_2} \wedge A_4$	32 ($= 2^5$)	33-64
Always-survivors if $U = 1$ but protectable if $U = 0$	$\overline{A_1} \wedge A_2 \wedge A_4$	32 ($= 2^5$)	97-128

Abbreviation: SACE, survivor average causal effect.

In the column *Possible risk-status types*, the numbers refer to risk-status types listed in Table S1.

^aNote that among the subpopulation with $U = 1$, always-survivors (ie, risk-status types 33-64, 97-256) are decomposed to the always-survivors irrespective of U (ie, risk-status types 129-256), never-survivors if $U = 0$ (ie, risk-status types 33-64), and protectable if $U = 0$ (ie, risk-status types 97-128).

$X = 1, U = 1] - E[Y|S = 1, X = 0, U = 1]$ can be expressed as shown below:

$$\begin{aligned}
 & E[Y|S = 1, X = 1, U = 1] - E[Y|S = 1, X = 0, U = 1] \\
 &= \Pr((B_1 \vee B_2 \vee B_4 \vee B_6) | (A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U) \\
 &\quad - \Pr((B_1 \vee B_4) | (A_1 \vee A_4) \wedge U) \\
 &= \Pr((B_1 \vee B_4) | (A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U) \\
 &\quad - \Pr((B_1 \vee B_4) | (A_1 \vee A_4) \wedge U),
 \end{aligned}$$

where the first equality follows from the definitions of the background factors and from the fact that we assume randomization of X , and the second equality follows from the assumption that among the individuals with $U = 1$ who are susceptible to A_1 or A_4U , only those with $(B_1 \vee B_4) \vee (\overline{B_2} \wedge \overline{B_6})$ may be present in the population (Figure 3), and the intersection of $(B_1 \vee B_4) \vee (\overline{B_2} \wedge \overline{B_6})$ and $(B_1 \vee B_2 \vee B_4 \vee B_6)$ is $(B_1 \vee B_4)$. Thus, the crude estimand is null if $(B_1 \vee B_4)$ is equally distributed among individuals with $((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U)$ and those with $((A_1 \vee A_4) \wedge U)$. Next, let us consider individuals aged 60 years or older ($U = 0$). If $\Pr(A_1 \wedge (\overline{B_1} \wedge B_2) \wedge \overline{U}) = 0$ holds, which means $SACE_{U=0}$ is null, $E[Y|S = 1, X = 1, U = 0] - E[Y|S = 1, X = 0, U = 0]$ can be expressed as shown below:

$$\begin{aligned}
 & E[Y|S = 1, X = 1, U = 0] - E[Y|S = 1, X = 0, U = 0] \\
 &= \Pr((B_1 \vee B_2) | (A_1 \vee A_2) \wedge \overline{U}) - \Pr(B_1 | A_1 \wedge \overline{U}) \\
 &= \Pr(B_1 | (A_1 \vee A_2) \wedge \overline{U}) - \Pr(B_1 | A_1 \wedge \overline{U}),
 \end{aligned}$$

where the first equality follows from the definitions of the background factors and from the fact that we assume randomization of X , and the

second equality follows from the assumption that among the individuals with $U = 0$ who are susceptible to A_1 , only those with $(B_1 \vee \overline{B_2})$ may be present in the population (Figure 3), and the intersection of $(B_1 \vee \overline{B_2})$ and $(B_1 \vee B_2)$ is B_1 . Thus, $E[Y|S = 1, X = 1, U = 0] - E[Y|S = 1, X = 0, U = 0]$ is null if B_1 is equally distributed among individuals with $((A_1 \vee A_2) \wedge \overline{U})$ and $(A_1 \wedge \overline{U})$. In the bottom part of Table 2, we provide expressions of some estimands including $E[Y|S = 1, X = 1] - E[Y|S = 1, X = 0]$ in terms of background factors A_k and B_k as well as U .

Discussion

The description of truncation by death under the potential outcomes framework, and specifically under principal stratification, represented an important methodological advance and led to the development of analytical approaches that can be used in this context.¹¹⁻¹⁴ The sufficient-cause framework, in its turn, breaks down causal processes into a finer level of causal mechanisms, which can then be interpreted as determining potential outcomes. As shown in the previous sections, the use of this latter framework to study truncation by death allows: (1) a different interpretation of the frequently reported estimand that conditions on observed survival, whose noncausal nature can also be understood in terms of risk-status types that only contribute data to 1 of the 2 terms in the comparison; (2) a detailed characterization of the distributional properties of sufficient causes that are captured by the SACE (see Tables 1 and 2); and (3) establishing conditions defined in terms of sufficient causes under which the causal estimand SACE is equal to zero. Furthermore, the derivation of the expressions for the SACE in terms of the background factors could be viewed as an extension of the previous work on the relation between the magnitude of standard causal effects (ie, causal effects that do not condition on joint potential outcomes) and the frequencies of background factors.^{24,33} Given this, we believe that the sufficient-cause framework, which has been used for decades

Table 2 Estimands for truncation by death with a common cause of survival and the outcome.

Estimands and its terms	Expressions in terms of background factors and U
$E[S X = 1]$	$\Pr((A_1 \vee A_2) \wedge \bar{U}) + \Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U)$
$E[S X = 0]$	$\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)$
$E[S X = 1] - E[S X = 0]$	$\{\Pr((A_1 \vee A_2) \wedge \bar{U}) - \Pr(A_1 \wedge \bar{U})\} + \{\Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U) - \Pr((A_1 \vee A_4) \wedge U)\}$
$\Pr(S^1 = 1, S^0 = 1)$	$\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)$
$E[Y^1 S^1 = 1, S^0 = 1]$	$\frac{\Pr(A_1 \wedge (B_1 \vee B_2) \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_2 \vee B_4 \vee B_6) \wedge U)}{\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)}$
$E[Y^0 S^1 = 1, S^0 = 1]$	$\frac{\Pr(A_1 \wedge B_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_4) \wedge U)}{\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)}$
$E[Y^1 - Y^0 S^1 = 1, S^0 = 1]$	$\frac{(\Pr(A_1 \wedge (B_1 \vee B_2) \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_2 \vee B_4 \vee B_6) \wedge U)) - (\Pr(A_1 \wedge B_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_4) \wedge U))}{\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)}$
$E[Y^1 - Y^0 S^1 = 1, S^0 = 1, U = 1]$	$\frac{\Pr((A_1 \vee A_4) \wedge (B_1 \vee B_2 \vee B_4 \vee B_6) \wedge U) - \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_4) \wedge U)}{\Pr((A_1 \vee A_4) \wedge U)}$
$E[Y^1 - Y^0 S^1 = 1, S^0 = 1, U = 0]$	$\frac{\Pr(A_1 \wedge (B_1 \vee B_2) \wedge \bar{U}) - (\Pr(A_1 \wedge B_1 \wedge \bar{U}))}{\Pr(A_1 \wedge \bar{U})}$
$E[Y S = 1, X = 1]$	$\frac{\Pr((A_1 \vee A_2) \wedge (B_1 \vee B_2) \wedge \bar{U}) + \Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge (B_1 \vee B_2 \vee B_4 \vee B_6) \wedge U)}{\Pr((A_1 \vee A_2) \wedge \bar{U}) + \Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U)}$
$E[Y S = 1, X = 0]$	$\frac{\Pr(A_1 \wedge B_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_4) \wedge U)}{\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)}$
$E[Y S = 1, X = 1] - E[Y S = 1, X = 0]$	$\frac{\Pr((A_1 \vee A_2) \wedge (B_1 \vee B_2) \wedge \bar{U}) + \Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge (B_1 \vee B_2 \vee B_4 \vee B_6) \wedge U)}{\Pr((A_1 \vee A_2) \wedge \bar{U}) + \Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U)} - \frac{\Pr(A_1 \wedge B_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge (B_1 \vee B_4) \wedge U)}{\Pr(A_1 \wedge \bar{U}) + \Pr((A_1 \vee A_4) \wedge U)}$
$E[Y S = 1, X = 1, U = 1] - E[Y S = 1, X = 0, U = 1]$	$\frac{\Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge (B_1 \vee B_2 \vee B_4 \vee B_6) \wedge U)}{\Pr((A_1 \vee A_2 \vee A_4 \vee A_6) \wedge U)} - \frac{\Pr((A_1 \vee A_4) \wedge (B_1 \vee B_4) \wedge U)}{\Pr((A_1 \vee A_4) \wedge U)}$
$E[Y S = 1, X = 1, U = 0] - E[Y S = 1, X = 0, U = 0]$	$\frac{\Pr(A_1 \wedge B_1 \wedge \bar{U})}{\Pr(A_1 \wedge \bar{U})} - \frac{\Pr(A_1 \wedge B_1 \wedge \bar{U})}{\Pr(A_1 \wedge \bar{U})}$

Here, to simplify expressions, we use $\bar{U}$ to denote $U = 0$, and U to denote $U = 1$. Note also that, as we consider the setting of a randomized trial (see Section "The Principal Stratification Approach to Truncation By Death"), the joint distribution of the different background factors and U is the same for both exposed and unexposed individuals; that is, $(A_1, A_2, A_4, A_6, B_1, B_2, B_4, B_6, U) \perp\!\!\!\perp X$. For this reason, we omit the corresponding conjunctions with X and $\bar{X}$ in all the formulas below. Relatedly, note that the distribution of the background factors A_k and B_k might differ by levels of U . Note that the expressions above follow from the definitions of the background factors of sufficient causes, and the formula for conditional probabilities; this is evident in the U -level specific expressions.

Subpopulation with $U = 1$		Subpopulation with $U = 0$	
Always-survivors $((S^1, S^0) = (1, 1))$ among whom $SACE_{u=1}$ is null	Always-survivors $((S^1, S^0) = (1, 1))$ among whom $SACE_{u=1}$ is positive	Always-survivors $((S^1, S^0) = (1, 1))$ among whom $SACE_{u=0}$ is null	Always-survivors $((S^1, S^0) = (1, 1))$ among whom $SACE_{u=0}$ is positive
$(A_1 \vee A_4) \wedge \{(B_1 \vee B_4) \vee (\overline{B_2} \wedge \overline{B_6})\} \wedge U$	$(A_1 \vee A_4) \wedge \{(\overline{B_1} \wedge \overline{B_4}) \wedge (B_2 \vee B_6)\} \wedge U$	$A_1 \wedge (B_1 \vee \overline{B_2}) \wedge \overline{U}$	$A_1 \wedge (\overline{B_1} \wedge B_2) \wedge \overline{U}$
Protectable $((S^1, S^0) = (1, 0))$		Protectable $((S^1, S^0) = (1, 0))$	
$(\overline{A_1} \wedge \overline{A_4}) \wedge (A_2 \vee A_6) \wedge U$		$\overline{A_1} \wedge A_2 \wedge \overline{U}$	
Never-survivors $((S^1, S^0) = (0, 0))$		Never-survivors $((S^1, S^0) = (0, 0))$	
$(\overline{A_1} \wedge \overline{A_4}) \wedge (\overline{A_2} \wedge \overline{A_6}) \wedge U$		$\overline{A_1} \wedge \overline{A_2} \wedge \overline{U}$	

Figure 3 Classification of individuals in terms of background factors and U under the sufficient cause positive monotonicity assumption.

to study key causal concepts in epidemiology,^{18,20-28,33-35} should also be considered in settings with post-treatment variable (here, survival)-related problems.

The rationale for focusing the results presented in this paper on $SACE_u$ is 2-fold: first, as mentioned above, membership to the always-survivors principal stratum might depend on the value of U ; second, for the outcome stage, some sufficient causes are dependent on U , indicating that these conditions are u -level specific. Note that the $SACE$ defined as a risk difference can be expressed as a weighted average of $SACE_u$ and is a directly collapsible effect measure.¹⁰

Our discussion above also showed that when we consider the 2 processes of survival and outcome, even if the conditions under which the $SACE$ is null hold, $E[Y|S = 1, X = 1] - E[Y|S = 1, X = 0]$ may not be null, even within strata of U . This occurs because risk-status types that correspond to non-null individual-level effect of X on S will only contribute data to 1 of these 2 terms that condition on observed survival, which clearly illustrates the noncausal nature of this estimand.

Another insight into this analysis is that, when considering the presence of possible mechanisms, that is, of sufficient causes, defined not only in terms of the exposure of interest, but also in terms of another cause of survival (here, the variable U), for some risk-status types, whether an individual is a member of the always-survivors stratum depends on the value of U . Put differently, given a population-level distribution of risk-status types, the relative frequencies of levels of U might influence the size of the always-survivors stratum in the population, and hence the public health relevance of the $SACE$. This detailed understanding of processes that contribute to survival, and consequently to principal stratum membership, might encourage descriptions of other questions studied under principal stratification³⁶ in the sufficient-cause framework. For instance, treatment adherence (or compliance), which differs from truncation by death in that the definability of the outcome is not dependent on the post-treatment variable, could also be studied under the sufficient-cause framework, possibly with explicit consideration of factors that influence adherence and the outcome. We note, however, that a potential limitation of the application of the sufficient-cause framework in truncation by death settings is that this causal framework is more naturally applicable to binary outcome variables, while in studies affected by truncation by death, the outcome of interest is sometimes quantitative (eg, a quality of life score). Here, it is worth mentioning that 1 possible extension of this work would involve a formulation of the sufficient cause model using hazard and/or cumulative rates³⁷ of death.

Taken together, our results suggest that explicit consideration of sufficient causes, even though detailed information on their components

is usually not available in real-world data, allows epidemiologists to better understand the mechanisms underlying this problem and the principal stratification approach to define effects in the presence of truncation by death.

Author contributions

Bronner P. Gonçalves (Conceptualization [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Writing—original draft [equal], Writing—review & editing [equal]), Eiji Yamamoto (Investigation [supporting], Methodology [supporting], Writing—review & editing [supporting]), and Etsuji Suzuki (Conceptualization [equal], Formal analysis [equal], Investigation [equal], Methodology [equal], Writing—original draft [equal], Writing—review & editing [equal])

Supplementary material

Supplementary material is available at *AJE Advances: Research in Epidemiology* online.

Conflicts of interest

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