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Identification and estimation of survivor average causal effects

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Abstract

In longitudinal studies, outcomes ascertained at follow-up are typically undefined for individuals who die prior to the follow-up visit. In such settings, outcomes are said to be truncated by death and inference about the effects of a point treatment or exposure, restricted to individuals alive at the follow-up visit, could be biased even if as in experimental studies, treatment assignment were randomized. To account for truncation by death, the survivor average causal effect (SACE), defines the effect of treatment on the outcome for the subset of individuals that would have survived regardless of exposure status. In this paper, the author nonparametrically identifies SACE by leveraging post-exposure longitudinal measurements that simultaneously mediate the effects of exposure on survival and on the outcome of interest. Nonparametric identification is achieved by supposing that the longitudinal data arise from a certain nonparametric structural equations model (NPSEM), and by making the monotonicity assumption that the effect of exposure on survival agrees in its direction across individuals. A novel weighted analysis involving a consistent estimate of the survival process, is shown to produce consistent estimates of SACE. A data illustration is given and the methods are extended to the context of time-varying exposures. We discuss a sensitivity analysis framework that relaxes assumptions about independent errors in the NPSEM, and may be used to assess the extend to which inference may be altered by a violation of key identifying assumptions.

1 Introduction

In longitudinal studies, it sometimes happens that individuals die between follow-up visits, in which case, unobserved outcomes that would have been ascertained during follow-up are said to be truncated by death. It is well known that inference about the effects of a point treatment

or exposure, restricted to individuals alive at a follow-up visit, could be biased even if as in experimental studies, treatment assignment were randomized. Similarly, it may be that a vaccine studied in a randomized trial, has a protective effect against a viral infection for some but not all individuals in the study. Then, viral load associated with the infection would not be observed unless a person became infected, which is a post-randomization event. As for truncation by death, an evaluation of the effects of the vaccine on viral load among infected individuals in the study likewise could be biased. Such bias may be present, if as we expect is likely the case in the aforementioned settings, there are downstream effects of the exposure or treatment, that independently affect survival or post-randomization infection, and the outcome of interest. A more fundamental issue is that the outcome may not be well defined for individuals who die, or remain un-infected by the virus, under either exposure status, and therefore, it is not clear that a causal effect of the exposure can be defined for such individuals. In order to appropriately account for truncation by death, one can define the survivor average causal effect (SACE), which is the effect of exposure on the outcome for the subset of individuals that would have survived regardless of [exposure status [1,2]. SACE is an instance of what is sometimes referred to as a principal strata causal effect [2,3,4]. An analogous principal strata causal effect is likewise defined for the effect of vaccine on viral load, among infected individuals for whom the vaccine has no protective effect against infection [5-8]. Throughout the paper, we refer to these two types of effects as SACE without further distinguishing between their respective contexts. In this paper, SACE is shown to be nonparametrically identified by leveraging post-exposure longitudinal measurements that simultaneously mediate the effects of exposure on survival and on the outcome of interest. Nonparametric identification is achieved by supposing that the longitudinal data arise from a certain nonparametric structural equations model [9], and by making the monotonicity assumption that the effect of exposure on survival agrees in its direction across individuals. Under these assumptions, a novel yet simple weighted

analysis with weights involving the survival process, is shown to produce consistent estimates of SACE, provided that the survival process is estimated consistently. A number of alternative estimators are also described, some with interesting theoretical properties. However, it is argued these other estimators may be more difficult to implement in practice, particularly in studies with longer follow-up, where the simple weighted analysis extends with little additional computational difficulty. An illustration of the simple weighted analysis is given in an application concerning the effects of smoking history on decline of cognitive function in an aging population subject to truncation by death. A general sensitivity analysis technique is described, to assess the extent to which inference might be affected by a violation of an assumption that all common causes of survival and the outcome are fully observed. Finally, in the context of time-updated exposures, the survivor marginal structural model (SMSM) is introduced, which amounts to a standard marginal structural model for the subpopulation that would survive irrespective of treatment history. A weighted approach is described for estimating the parameters of an SMSM.

2 A simple three-occasion study

2.1 Causal diagram interpretation of biased analyses

By way of introduction, first consider a simplified version of the study of the effects of smoking on cognitive function decline, here restricted to only three longitudinal occasions, as depicted in the causal diagram in Figure 1.

Insert Figure 1.

The simplified design consists of a baseline $j = 0$ at which binary smoking status A is observed, and two follow-up contacts, with cognitive function and other covariates assessed at each $j = 1, 2$.

Until otherwise stated, assume that all respondents participate at the first follow-up and thus data $\mathbf{C}_1$ are collected for all subjects at $j = 1$, but some individuals die before the second follow-up, with $S = 1$ indicating survival. Suppose that besides for cognitive function, $\mathbf{C}_1$ includes all other effects of smoking, that may simultaneously affect survival and the outcome Y corresponding to cognitive decline between $j = 1$ and $j = 2$; examples of such variables are listed in Section 4. In addition, assume that survival may be directly affected by A and further assume that death is the only source of attrition in this study. Throughout, we assume no measurement error. The double-headed arrow between $\mathbf{C}_1$ and Y encodes possible unmeasured common causes of say cognitive function at follow-up and change in cognitive function Y, the presence of which cannot be ruled out with certainty. For instance, there is evidence for genetic determinants of Alzheimer's disease that suggests a genetic basis for an individual's cognitive function over time [10]; however, such genetic information is not available in this study. Although such a genetic component would not be directly affected by smoking behavior, unmeasured common causes of cognitive function $\mathbf{C}_1$ and subsequent decline of cognitive function Y, might also include unknown epigenetic effects of smoking behavior on future cognitive function, and therefore, could be directly affected by smoking. For simplicity, we further assume until later sections that all analyses are stratified by pre-exposure confounders of A, which is suppressed in the notation, such that the effects of A on $(\mathbf{C}_1, Y, S)$ are unconfounded, and therefore A behaves as if it were randomized.

The causal diagram in Figure 1 can be used to formalize the bias associated with an analysis of the effects of baseline smoking status A on cognitive function decline Y, conditional on being alive at the end of follow-up. To understand how this bias arises, it suffices to note that by d-separation [9], such an analysis would unblock the non-causal pathways $A \rightarrow S \leftarrow \mathbf{C}_1 \rightarrow Y$ and $A \rightarrow \mathbf{C}_1 \leftrightarrow Y$, thus indicating an effect of smoking on cognitive decline even if there were none. One should also note that further conditioning on $\mathbf{C}_1$ does not resolve the difficulty, since doing

so does not block the pathway $A \rightarrow \mathbf{C}_1 \leftrightarrow Y$. Both of these strategies essentially fail because conditioning on S implies conditioning on a collider on the pathway $A \rightarrow S \leftarrow \mathbf{C}_1 \rightarrow Y$ as in the first strategy, but also implies conditioning on a direct descendant of a collider on the pathway $A \rightarrow \mathbf{C}_1 \leftrightarrow Y$, which induces non-causal associations between A and Y [9]. Further conditioning on $\mathbf{C}_1$ as in the second strategy above does not really help resolve this issue since it also implies conditioning on a collider on the pathway $A \rightarrow \mathbf{C}_1 \leftrightarrow Y$. Collider bias is invariably the pitfall, and thus a source of bias, for most analyses involving conditioning on a post-exposure event.

2.2 Nonparametric structural equations model

The following exposition is framed around a structural equation theory of causal inference, described by Pearl [9]. Structural equations provide a nonparametric algebraic interpretation of the diagram of Figure 1 corresponding to four functions, one for each variable on the causal graph:

$$A = g_A\left(\varepsilon_A\right); \tag{1}$$

$$\mathbf{C}_1 = \mathbf{g}_{\mathbf{C}_1}(A, \varepsilon_{\mathbf{C}_1}); \tag{2}$$

$$S = g_S\left(A, \mathbf{C}_1, \varepsilon_S\right); \tag{3}$$

$$Y = \begin{cases} g_Y\left(A, \mathbf{C}_1, \varepsilon_Y\right) & \text{if } S = 1 \\ \text{undefined} & \text{if } S = 0 \end{cases} \tag{4}$$

Each of the nonparametric functions $\{g_A, ..., g_Y\}$ represents a causal mechanism that determines the value of the left variable, known as the output, from variables on the right, known as the inputs [9]. The errors $(\varepsilon_A, \varepsilon_{\mathbf{C}_1}, \varepsilon_S, \varepsilon_Y)$ stand for all factors not included on the graph that could possibly affect their corresponding outputs when all other inputs are held constant. For instance,

ε_S includes all causes of death unrelated to cognitive function decline. To be consistent with the causal graph presented in Figure 1, we require that the errors $(\varepsilon_A, \varepsilon_S)$ be mutually independent, and we require that they be jointly independent of $(\varepsilon_{\mathbf{C}_1}, \varepsilon_Y)$. However, as indicated by the double arrow edge in Figure 1, $\varepsilon_{\mathbf{C}_1}$ may not be independent of ε_Y. We allow all error distributions to otherwise remain arbitrary. Lack of a causal effect of a given variable on an output is encoded by an absence of the variable from the right-hand side. For example, the absence of a direct effect of smoking on cognitive function at the first follow-up would imply removing A from the arguments of $\mathbf{g}_{\mathbf{C}_1}$ encoding the assumption that variations in A leave $\mathbf{C}_1$ unchanged, as long as $\varepsilon_{\mathbf{C}_1}$ remains constant, which is consistent with the assumption that there is no unmeasured common cause of smoking and cognitive function.

The last equation makes explicit the fact that Y is observed only among survivors with $(S = 1)$, with corresponding structural equation $g_Y(A, \mathbf{C}_1, \varepsilon_Y)$. As stated by Pearl [9], the invariance of structural equations permits their use as a basis for modeling causal effects and counterfactuals. In fact, to emulate the intervention in which one sets $\{A = a\}$ for all individuals simply amounts to replacing the equation for A with $A = a$, producing the following set of modified equations:

$$A = a; \tag{5}$$

$$\mathbf{C}_1(a) = \mathbf{g}_{\mathbf{C}_1}(a, \varepsilon_{\mathbf{C}_1}); \tag{6}$$

$$S(a) = g_S(a, \mathbf{C}_1(a), \varepsilon_{\mathbf{S}}); \tag{7}$$

$$Y(a) = \begin{cases} g_Y(a, \mathbf{C}_1(a), \varepsilon_Y) & \text{if } S(a) = 1 \\ \text{undefined} & \text{if } S(a) = 0 \end{cases} \tag{8}$$

with $(\mathbf{C}_1(a), S(a), Y(a))$ denoting the counterfactual outcomes had smoking status been set to a (possibly contrary to fact). We emphasize that while the model specifies a structural equation for

survival, survival is not manipulable, and, together with Y, should be understood as part of the outcome produced by the system of equations. As previously observed [11], structural equations are particularly helpful to clarify the difficulty with interpreting the effect of smoking when truncation by death is present. Specifically, we note that the individual effect of smoking is recovered by taking the contrast $Y(a = 1) - Y(a = 0)$, which clearly is defined only for individuals in the principal stratum $\{S(0) = S(1) = 1\}$ and is equal to

$$g_Y\left(1, \mathbf{C}_1\left(1\right), \varepsilon_Y\right) - g_Y\left(0, \mathbf{C}_1\left(0\right), \varepsilon_Y\right)$$

and the associated population average gives the SACE estimand denoted β:

$$\begin{aligned}\beta &= \mathbb{E}\left\{Y(a=1) - Y(a=0) | S(a=0) = S(a=1) = 1\right\} \\ &= \mathbb{E}\left\{g_Y\left(1, \mathbf{C}_1\left(1\right), \varepsilon_Y\right) - g_Y\left(0, \mathbf{C}_1\left(0\right), \varepsilon_Y\right) | S(a=0) = S(a=1) = 1\right\}\end{aligned}$$

SACE is generally not identified without additional assumptions, even under an NPSEM. At one end of the spectrum of possible identifying assumptions, one might assume that the sharp null hypothesis holds, that for all individuals in the population, A has no individual causal effect on survival,.i.e. $S(a = 1) = S(a = 0) = 1$ almost surely. The assumption implies that individuals who survive under an exposure status constitute a random sample of individuals who would survive irrespective of exposure value. Then, it is straightforward to verify that:

$$\beta = \mathbb{E}\left(Y | S = 1, A = 1\right) - \mathbb{E}\left(Y | A = 0, S = 1\right).$$

In light of existing scientific evidence about the harmful effects of smoking on human health, the above identifying assumption of no individual causal effect of smoking on survival is clearly

inappropriate, and therefore the above equation is unlikely to be correct.

At the opposite end of the spectrum of possible identifying assumptions, a strategy that is sometimes adopted entails performing a sensitivity analysis, using data on (A, SY, S) [7,12,13,14], possibly also incorporating pre-exposure covariates [9]. A sensitivity analysis then typically involves recovering an estimate of SACE upon making a monotonicity assumption about the effects of exposure on survival, and by fixing certain non-idendified parameters involving the joint distribution of potential outcomes to some hypothetical value, which is then varied over a certain range to assess the degree to which the effect estimate of SACE changes as a function of these parameters. Worst-case scenarios of a sensitivity analysis give rise to bounds for SACE, but such bounds typically only apply in rather simple settings [3,15].

An alternative identifying assumption that is sometimes made in the principal strata literature, and that falls somewhere in between the above extremes, involves assuming that certain potential outcome independencies about the outcome of interest and survival, can be obtained upon conditioning on enough pre-exposure covariates, such that SACE becomes identified within levels of such covariates [16,17] proposed to identify SACE under a parametric model and presented the maximum likelihood estimation. They discussed identifiability for a mixture normal model; however as pointed out by Ding et al [18], the mixture normal model may not be identifiable under the extreme case that the probability of each latent component is the same . When the outcome of interest is binary, even with a parametric binary mixture model, the causal parameter of interest is still not identifiable without some further assumptions [18]. An alternative approach is given by Ding et al [18] who exploit a form of exclusion restriction assumption for an observed pre-exposure covariate to obtain nonparametric identification of SACE. Nolen and Hudgens [19] proposed an elegant randomization-based approach about causal effects within principal strata -possibly within pre-exposure covariate levels- that is particularly useful for testing the null hypothesis of no prin-

cipal strata causal effect but relies for identification and estimation away from the null, on the assumption of a constant individual principal strata causal effect.

The aforementioned methods all share a notable limitation, in that none appears to appropriately incorporate risk factors of survival available in post-exposure follow-up. In our hypothetical example, it is unclear whether these methods, including sensitivity analysis techniques, can make use of follow-up data collected in $\mathbf{C}_1$ such as post exposure cognitive function, a correlate of survival that is likely affected by smoking status. A somewhat related context to ours is considered by Dai et al [20], who develop a partially hidden markov model for time-varying principal stratification in HIV prevential trials. Their proposed approach however relies on a categorization of the intermediate variables into discrete event types and therefore does not easily generalize for continuous or high dimensional intermediate variables. Tchetgen Tchetgen et al [11] provide an alternative interpretation of standard inverse probability weighting for dependent censoring, incorporating time-updated covariates. They show that under the NPSEM defined by equations (1-4), the causal effect identified by inverse-probability weighting survivors, in fact, naturally incorporates principal-strata causal effects, therefore, formally establishing a previously unknown relation between inverse-probability weighting and principal stratification, two seemingly unrelated analytic frameworks. However, their proposed model does not identify SACE exactly without an additional assumption. In the next section, an alternative approach is proposed that does not suffer from these possible limitations. But first, we refine the usual definition of SACE, to rule out certain pathological situations. As discussed above, SACE is typically defined to be the average exposure effect for individuals that would survive irrespective of exposure. One might further refine the definition of SACE by considering a person's survival status $S(e = 1, \mathbf{C}_1(e = 0))$ in the hypothetical scenario where the person smoked, but $\mathbf{C}_1$ behaved as if the individual did not smoke; likewise one could consider a person's survival status $S(e = 0, \mathbf{C}_1(e = 1))$ in the hypothetical scenario

where the person did not smoke but $\mathbf{C}_1$ behaved as if the person smoked. Such "cross-world" potential outcomes feature prominently in recent literature on causal mediation analysis, where they are used for formal causal definitions of direct and indirect effects of an exposure (see [21,22]). Consider the following combination of an individual's potential outcomes

$$\left\{ \begin{array}{c} S(e=0) = S(e=0, \mathbf{C}_1(e=0)), S(e=1, \mathbf{C}_1(e=0)), \\ S(e=0, \mathbf{C}_1(e=1)), S(e=1) = S(e=1, \mathbf{C}_1(e=1)) \end{array} \right\}$$

which allows further distinction between individuals who would survive irrespective of exposure, i.e. $S(e=0) = S(e=1) = 1$. For instance, it may be that a person that would survive whether exposed or not, would not survive in certain cross-world situations $S(e=1, \mathbf{C}_1(e=0)) = S(e=0, \mathbf{C}_1(e=1)) = 0$. Such an individual would be considered rather unusual and hereafter the causal effect of exposure for such a person is not further considered, and SACE is redefined to be the causal effect of exposure for individuals that would survive regardless of exposure, including under cross-world situations:

$$\psi = \mathbb{E}\left\{Y(a=1) - Y(a=0) | S(a, \mathbf{C}_1(a^*)) = 1; a,\ a^* \in \{0,1\}\right\}.$$

If one were to a priori rule out the possibility that an individual that would survive irrespective of exposure status, could die under cross-world conditions, then it would also be that $\psi = \beta$, and therefore the more stringent definition of SACE would match the more common definition.

2.3 Identification of SACE

Identification of SACE requires, in addition to the NPSEM assumptions, that we make the following assumptions:

Monotonicity Assumption:

$$S(a=1,\mathbf{C}_1(a^*)) \leq S(a=0,\mathbf{C}_1(a^*)) \textit{ almost surely, } a^*=0,1$$

The contrast $S(a=1,\mathbf{C}_1(a^*)) - S(a=0,\mathbf{C}_1(a^*))$ is known in the causal mediation literature as the pure or natural direct effect of exposure, in a hypothetical situation where $\mathbf{C}_1$ is set to what it would be under smoking status a^*, and captures the direct effects of exposure not mediated by $\mathbf{C}_1$. Thus, the assumption states that there is no individual in the population, for whom smoking provides a protective individual direct effect on survival.

In order to state the second assumption, consider the following subsets of individuals. Let $\mathcal{P}_0$ denote the subset of individuals that would survive regardless of smoking, in a hypothetical situation where $\mathbf{C}_1$ would behave as if they did not smoke i.e. $S(a=0,\mathbf{C}_1(a=0)) = S(a=1,\mathbf{C}_1(a=0)) = 1$, and let $\mathcal{P}_1$ denote the subset of individuals that would survive irrespective of smoking, in a hypothetical situation where $\mathbf{C}_1$ would behave as if they smoked, i.e. $S(a=0,\mathbf{C}_1(a=1)) = S(a=1,\mathbf{C}_1(a=1)) = 1$.

Concordant Survivorship Assumption : $\mathcal{P}_0 = \mathcal{P}_1$ *almost surely.*

This second assumption states that individuals that would survive irrespective of smoking status, in a hypothetical situation where $\mathbf{C}_1$ behaved as if they smoked, would also survive irrespective of smoking status, in the hypothetical situation where $\mathbf{C}_1$ behaved as if they did not smoke, and that the converse also holds.

Then we have the following result:

Theorem 1 *Under the NPSEM given by equations* $(1)-(4)$, *and under the Monotonicity As-*

sumption, and the Concordant Survivorship Assumption, we have that SACE :

$$\psi = \mathbb{E}\left\{Y(a=1) - Y(a=0) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\}$$

is nonparametricaly identified and is given by $\mu_1 - \mu_0$, *where*

$$\begin{aligned}
\mu_1 &= \mathbb{E}\left\{Y(a=1) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\} \\
&= \mathbb{E}\left\{Y(a=1) | S(a=0, \mathbf{C}_1(a=1)) = S(a=1, \mathbf{C}_1(a=1)) = 1\right\} \\
&= \mathbb{E}\left\{Y | A=1, S=1\right\}
\end{aligned}$$

and

$$\begin{aligned}
\mu_0 &= \mathbb{E}\left\{Y(a=0) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\} \\
&= \mathbb{E}\left\{Y(a=0) | S(a=0, \mathbf{C}_1(a=0)) = S(a=1, \mathbf{C}_1(a=0)) = 1\right\} \\
&= \frac{\int \mathbb{E}\left(Y | A=0, S=1, \mathbf{C}_1 = \mathbf{c}\right) \Pr(S=1 | A=1, \mathbf{C}_1 = \mathbf{c}) dF(\mathbf{c} | A=0)}{\int \Pr(S=1 | A=1, \mathbf{C}_1 = \mathbf{c}) dF(\mathbf{c} | A=0)},
\end{aligned} \tag{9}$$

where $F(u_1|u_2)$ *stands for the cumulative distribution function of* U_1 *given* U_2,*evaluated at* $U_1 = u_1$, $U_2 = u_2$, *and it is assumed that* $\Pr(S=1|A=1, \mathbf{C}_1 = \mathbf{c}) / \Pr(S=1|A=0, \mathbf{C}_1 = \mathbf{c}) < \infty$.

According to the theorem, estimation of the average survivor outcome for smoking presents no particular difficulty, and can be achieved by a simple average outcome of exposed individuals that survived. The situation is quite different for the average survivor outcome for nonsmoking. The theorem states that this average value can be obtained by using the expression given in equation (9). Intuition for this expression is gained by comparing it to that of the average outcome for

unexposed individuals that actually survived:

$$\mathbb{E}\left(Y|A=0,S=1\right)=\frac{\int \mathbb{E}\left(Y|A=0,S=1,\mathbf{C}_1=\mathbf{c}\right)\Pr(S=1|A=0,\mathbf{C}_1=\mathbf{c})dF(\mathbf{c}|A=0)}{\int \Pr(S=1|A=0,\mathbf{C}_1=\mathbf{c})dF(\mathbf{c}|A=0)}.$$

Then, one may note that the principal distinction between these two expressions is that the conditional survival probability for the unexposed used in both numerator and denominator of the second expression is replaced by that for the exposed in the first expression. This substitution essentially amounts to a form of standardization of unexposed individuals who survived, by the survival probability of exposed individuals with similar covariate history. One should note as well that in the special instance where $\mathbf{C}_1$ and A are both unrelated to survival, then, as one might expect, the two above expressions coincide. However, in general, the two functionals do not coincide, and the subtle difference between them has nontrivial implications for statistical inference. In particular, whereas estimation of $\mathbb{E}\left(Y|A=1,S=1\right)$ is fairly straightforward and does not require a first stage estimation of nuisance parameters, estimation of μ_0 is somewhat more involved.

2.4 Estimation of SACE

As explained in the previous section, we need only to consider estimation of μ_0. Ideally, we may wish to estimate this quantity nonparametrically, so as to reduce the risk of bias due to modeling error; however, this may not be possible in practice. That is because, as shown below, estimation of μ_0 is generally not possible without involving an estimate of a subset of the following quantities $\{\mathbb{E}\left(Y|A,S=1,\mathbf{C}_1\right),\Pr(S=1|A,\mathbf{C}_1),dF(\mathbf{C}_1|A)\}$. In practice, one would probably seek to enrich as much as possible the set of covariates in $\mathbf{C}_1$ so as to ensure that all variables are included, that potentially simultaneously mediate the effects of exposure on survival and on the outcome. As a result, our primary interest concerns settings where $\mathbf{C}_1$ potentially includes a large number of

covariates, a subset of which are possibly continuous, such that nonparametric methods for estimating the above density and regression models, such as smoothing techniques, may be of limited value. Consequently, next, we present three simple estimation strategies based on low dimensional models using iid data $(A, \mathbf{C}_1, S, SY)$. Let $\{\widehat{\mathbb{E}}(Y|A, S=1, \mathbf{C}_1), \widehat{\Pr}(S=1|A, \mathbf{C}_1), d\widehat{F}(\mathbf{C}_1|A)\}$ denote estimates obtained using parsimonious parametric working models for the unknown conditional mean and the two unknown conditional densities. The first strategy entails direct substitution of unknown quantities in (9) by their corresponding estimate, which gives

$$\widehat{\mu}_0^1 = \frac{\int \widehat{\mathbb{E}}(Y|A=0, S=1, \mathbf{C}_1=\mathbf{c}) \widehat{\Pr}(S=1|A=1, \mathbf{C}_1=\mathbf{c}) d\widehat{F}(\mathbf{c}|A=0)}{\int \widehat{\Pr}(S=1|A=1, \mathbf{C}_1=\mathbf{c}) d\widehat{F}(\mathbf{c}|A=0)}$$

This estimator depends heavily on correct specification of all three models. An alternative estimator that makes fewer assumptions is based on the following equivalent representation of μ_0

$$\begin{aligned} &\frac{\int \mathbb{E}(Y|A=0, S=1, \mathbf{C}_1=\mathbf{c}) \Pr(S=1|A=1, \mathbf{C}_1=\mathbf{c}) dF(\mathbf{c}|A=0)}{\int \Pr(S=1|A=1, \mathbf{C}_1=\mathbf{c}) dF(\mathbf{c}|A=0)} \\ &= \frac{\mathbb{E}\{\mathbb{E}(Y|A=0, S=1, \mathbf{C}_1) ASdF(\mathbf{C}_1|A=0)/dF(\mathbf{C}_1|A=1)\}}{\mathbb{E}\{ASdF(\mathbf{C}_1|A=0)/dF(\mathbf{C}_1|A=1)\}} \end{aligned}$$

where, throughout, it is assumed that $dF(\mathbf{C}_1|A=0)/dF(\mathbf{C}_1|A=1) < \infty$ almost surely, $a \neq a^*$, which gives the estimator:

$$\widehat{\mu}_0^2 = \frac{\mathbb{P}_n\left[\widehat{\mathbb{E}}(Y|A=0, S=1, \mathbf{C}_1) AS\left\{d\widehat{F}(\mathbf{C}_1|A=0)/d\widehat{F}(\mathbf{C}_1|A=1)\right\}\right]}{\mathbb{P}_n\left[AS\left\{d\widehat{F}(\mathbf{C}_1|A=0)/d\widehat{F}(\mathbf{C}_1|A=1)\right\}\right]}$$

where $\mathbb{P}_n(\cdot) = n^{-1}\sum_i (\cdot)_i$. This second approach improves over the first in terms of robustness, since it does not directly involve an estimate of the survival process. Finally, consider yet another

representation of μ_0 :

$$\frac{\int \mathbb{E}\left(Y|A=0,S=1,\mathbf{C}_1=\mathbf{c}\right)\Pr(S=1|A=1,\mathbf{C}_1=\mathbf{c})dF(\mathbf{c}|A=0)}{\int \Pr(S=1|A=1,\mathbf{C}_1=\mathbf{c})dF(\mathbf{c}|A=0)}$$
$$=\frac{\mathbb{E}\left\{Y(1-A)S\Pr(S=1|A=1,\mathbf{C}_1)/\Pr(S=1|A=0,\mathbf{C}_1)\right\}}{\mathbb{E}\left\{(1-A)S\Pr(S=1|A=1,\mathbf{C}_1)/\Pr(S=1|A=0,\mathbf{C}_1)\right\}} \tag{10}$$

which motivates the estimator :

$$\widehat{\mu}_0^3=\frac{\mathbb{E}\left\{Y(1-A)S\widehat{\Pr}(S=1|A=1,\mathbf{C}_1)/\widehat{\Pr}(S=1|A=0,\mathbf{C}_1)\right\}}{\mathbb{E}\left\{(1-A)S\widehat{\Pr}(S=1|A=1,\mathbf{C}_1)/\widehat{\Pr}(S=1|A=0,\mathbf{C}_1)\right\}}$$

This last estimator has the advantage that it only requires an estimate of the survival process, and both the outcome regression and the covariates distribution are left unrestricted. Thus of the three approaches presented above, the last is most appealing in terms of modeling requirement, since it involves a single model versus the other two approaches that involve using more than one model. Furthermore, as shown in the next section, the third strategy naturally extends to a general longitudinal context with arbitrary follow-up time, with little extra difficulty. We do not further consider the first two approaches on the above theoretical grounds, although in Section 5, a doubly robust approach is given, that combines some of the above strategies such that consistent estimation of μ_0 remains possible even under partial model mis-specification, i.e. when only some but not all required models are correctly specified.

3 Longitudinal studies of arbitrary length

3.1 Longitudinal NPSEM and identification of SACE

We turn to the more general context of a longitudinal study with potentially more than two follow-up visits $j = 0, ...J$, where $J \geq 2$ is fixed, and at each occasion j, one observes $(S_j, S_j \mathbf{C}_j)$, where S_j indicates survival status at time j, and $\mathbf{C}_j$ includes covariates measured at time j. We suppose that $S_0 = S_1 = 1$, and therefore, a vector of pre-exposure covariates $\mathbf{C}_0$ is measured on all individuals in the target population; and exposure A is measured concurrently with covariates $\mathbf{C}_1$ on all individuals in the target population. The variable $\mathbf{C}_J = Y$ encodes the outcome measured at the end of follow-up. We consider the general NPSEM:

$$\text{For } j = 0, \tag{11}$$

$$\mathbf{C}_0 = \mathbf{g}_{\mathbf{C}_0}(\varepsilon_{\mathbf{C}_0});$$

$$\text{for } j = 1,$$

$$\begin{cases} \mathbf{C}_1 = \mathbf{g}_{\mathbf{C}_1}(\varepsilon_{\mathbf{C}_1}, \mathbf{C}_0); \\ A = g_A(\varepsilon_A, \mathbf{C}_0); \end{cases} \tag{12}$$

$$\text{and for } j = 2, ..., J$$

$$S_j = \begin{cases} g_{S_j}\left(A, \overline{\mathbf{C}}_{j-1}, \varepsilon_{S_j}\right) & \text{if } S_{j-1} = 1; \\ 0 & \text{if } S_{j-1} = 0; \end{cases} \tag{13}$$

$$\mathbf{C}_j = \begin{cases} \mathbf{g}_{\mathbf{C}_j}(A, \overline{\mathbf{C}}_{j-1}, \varepsilon_{\mathbf{C}_j}) & \text{if } S_j = 1; \\ \text{undefined} & \text{if } S_j = 0. \end{cases} \tag{14}$$

We assume that

$$\varepsilon_A \perp\!\!\!\perp \left\{\varepsilon_{s_j} : j = 2, ..., J\right\},$$

and we also assume that:

$$\left\{\varepsilon_A, \varepsilon_{s_j} : j = 2, ..., J\right\} \perp\!\!\!\perp \left\{\varepsilon_{\mathbf{C}_j} : j \geq 2\right\}$$

However, $\varepsilon_{\mathbf{C}_j}$ and $\varepsilon_{\mathbf{C}_{j'}}$ may be dependent, and ε_{s_j} and $\varepsilon_{s_{j'}}$ may be dependent, $j \neq j'$. The causal diagram of Figure 2 depicts the observed data, generated under such an NPSEM for an individual alive at the end of follow-up, in the special case where $J = 4$. We allow all error distributions to otherwise remain arbitrary.

Insert Figure 2.

This more general NPSEM extends the previous model, to accommodate, both confounding by pre-exposure covariates $\mathbf{C}_0$, and longitudinal data $\overline{\mathbf{C}}_J$, where $\overline{\mathbf{C}}_j$ denotes the history $(\mathbf{C}_0, ..., \mathbf{C}_j)$. Note that because $\mathbf{C}_0$ and $\mathbf{C}_1$ are respectively prior to and concurrent with exposure A, they cannot be affected by exposure, and thus $\mathbf{C}_0(a) = \mathbf{C}_0$ and $\mathbf{C}_1(a) = \mathbf{C}_1$. Technically, $\mathbf{C}_0$ confounds the effects of A, but $\mathbf{C}_1$ is not considered a confounder even though it may be correlated with A, and may be used to account for the bias due to truncation by death. Crucially, independence of $\varepsilon_{\mathbf{C}_{j-1}}$ and ε_{s_j} implies that for individuals alive at time $j-1$, $\left(\overline{\mathbf{C}}_{j-2}, A\right)$ intercepts or block all non-causal pathways between $\mathbf{C}_{j-1}$ and S_j; in the language of causal graphs, $\left(\overline{\mathbf{C}}_{j-2}, A\right)$ is said to block all back-door paths from $\mathbf{C}_{j-1}$ to S_j.

SACE is defined to be the causal effect of exposure on an outcome measured at the end of follow-up, among individuals that would survive whether exposed or not, and with the covariate

history they would experience under possibly conflicting exposure status:

$$\psi_J = \mathbb{E}\left\{Y(a=1) - Y(a=0) | S_J(a, \overline{\mathbf{C}}_{J-1}(a^*)) = 1;\ a, a^* \in \{0,1\}\right\}$$

As previously mentioned in the 3-occasion case, here we again have that $S_J(0, \overline{\mathbf{C}}_{J-1}(0))S_J(1, \overline{\mathbf{C}}_{J-1}(1)) = 1$ implies that $S_J(0, \overline{\mathbf{C}}_{J-1}(1))S_J(1, \overline{\mathbf{C}}_{J-1}(0)) = 1$ almost surely, then

$$\psi_J = \mathbb{E}\left\{Y(a=1) - Y(a=0) | S_J(a, \overline{\mathbf{C}}_{J-1}(a)) = S_J(a) = 1;\ a \in \{0,1\}\right\}$$

which matches SACE as commonly defined in the literature.

Identification requires an extension of the Monotonicity and Concordant Survivorship assumptions:

<u>*Sequential Monotonicity Assumption for Point Exposure*</u>:

$$\text{if } S_{j-1}(1, \overline{\mathbf{C}}_{j-2}(a))S_{j-1}(0, \overline{\mathbf{C}}_{j-2}(a)) = 1 \text{ then } S_j(1, \overline{\mathbf{C}}_{j-1}(a)) \leq S_j(0, \overline{\mathbf{C}}_{j-1}(a))$$

$$\textit{almost surely; } a = 0, 1,\ \ j = 1, ..., J$$

Let $\mathcal{P}_{0,J}$ denote the subset of individuals that would survive until the end of follow-up regardless of smoking, in a hypothetical situation where $\overline{\mathbf{C}}_J$ would behave as if they did not smoke, and let $\mathcal{P}_{1,J}$ denote the subset of individuals that would survive irrespective of smoking, in a hypothetical situation where $\overline{\mathbf{C}}_J$ would behave as if they smoked.

<u>*Concordant Survivorship Assumption for Point Exposure* :</u>

$$\mathcal{P}_{0,J} = \mathcal{P}_{1,J} \text{ almost surely.}$$

The Sequential Monotonicity Assumption states that for a person that would survive up to time $j-1$ irrespective of smoking status, in the hypothetical situation where his covariate history behaves as if smoking status were fixed to a, if the person were to survive at time j when exposed and with covariate history as if smoking status were equal to a, the person would also survive at time j, with similar covariate history, if he were not to smoke. The Concordant Survivorship Assumption essentially states that

$$S_J(1, \overline{\mathbf{C}}_{J-1}(0))S_J(0, \overline{\mathbf{C}}_{J-1}(0)) = 1 \iff S_J(1, \overline{\mathbf{C}}_{J-1}(1))S_J(0, \overline{\mathbf{C}}_{J-1}(1)) = 1 \text{ almost surely}$$

which is the natural extension of the previous Concordant Survivorship Assumption. Throughout, we further assume that

$$\prod_{k=2}^{J} \pi_k\left(1, \overline{\mathbf{C}}_{k-1}\right) / \prod_{k=2}^{J} \pi_k\left(0, \overline{\mathbf{C}}_{k-1}\right) < \infty$$

almost surely and $0 < p\left(\mathbf{C}_0\right) < 1$ almost surely.

Then we have the following result:

Theorem 2 *Under the NPSEM given by equations* $(11)-(14)$, *the Sequential Monotonicity Assumption and the Concordant Survivorship Assumption for point exposure; we have that* ψ_J *is nonparametricaly identified and is given by* $\mu_{1,J} - \mu_{0,J}$, *where*

$$\begin{aligned}\mu_{1,J} &= \mathbb{E}\left\{Y(a=1)|S_J(a, \overline{\mathbf{C}}_{J-1}(a^*)) = 1;\ a, a^* \in \{0,1\}\right\} \\ &= \mathbb{E}\left(Y|A=1, S_J=1\right),\end{aligned}$$

and

$$\mu_{0,J} = \mathbb{E}\left\{Y(a=0)|S_J(a,\overline{\mathbf{C}}_{J-1}(a^*))=1;\ a,a^*\in\{0,1\}\right\}$$
$$= \frac{\int ... \int \mathbb{E}\left(Y|A=0,S_J=1,\overline{\mathbf{C}}_{J-1}=\overline{\mathbf{c}}_{J-1}\right)\prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{c}}_{j-1}\right)\prod_{j=0}^{J-1}dG_{0,j}(\mathbf{c}_j;\overline{\mathbf{c}}_{j-1})}{\int ... \int \prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{c}}_{j-1}\right)\prod_{j=0}^{J-1}dG_{0,j}(\mathbf{c}_j;\overline{\mathbf{c}}_{j-1})}, \tag{15}$$

where

$$\pi_j\left(a,\overline{\mathbf{c}}_{j-1}\right) = \Pr(S_j=1|A=a,\overline{\mathbf{C}}_{j-1}=\overline{\mathbf{c}}_{j-1},S_{j-1}=1), j=2,...J;$$

$$G_{a,j}(\mathbf{c}_j;\overline{\mathbf{c}}_{j-1}) = F(\mathbf{c}_j|A=a,\overline{\mathbf{C}}_{j-1}=\overline{\mathbf{c}}_{j-1},S_j=1),\ \ j=2,...,J-1;$$

$$G_{0,1}(\mathbf{c}_1;\overline{\mathbf{c}}_0) = G_{1,1}(\mathbf{c}_1;\overline{\mathbf{c}}_0) = F(\mathbf{c}_1|\mathbf{c}_0);$$

$$G_{0,0}(\mathbf{c}_0;\overline{\mathbf{c}}_{-1}) = G_{1,0}(\mathbf{c}_0;\overline{\mathbf{c}}_{-1}) = F(\mathbf{c}_0).$$

According to the theorem, as was the case in the 3-occasion example, estimation of the average survivor outcome for smoking likewise presents no particular difficulty, and can be achieved by a simple average of the outcomes of exposed individuals that survived until the end of follow-up. The theorem states that the average survivor outcome for nonsmoking is given by the functional in equation (15). This formula is a generalization of equation (9) that appropriately accounts for more lengthy follow-up, but also accounts for pre-exposure confounding by $\mathbf{C}_0$. Instead of a marginal SACE parameter, a conditional SACE parameter might be of interest, say:

$$\psi_J(v) = \mathbb{E}\left\{Y(a=1)-Y(a=0)|\mathbf{V}=\mathbf{v},S_J(a,\overline{\mathbf{C}}_{J-1}(a^*))=1;\ a,a^*\in\{0,1\}\right\}$$

where $\mathbf{V}\subset\mathbf{C}_0$ is a vector of pre-exposure confounders, such that $\mathbf{C}_0=(\mathbf{V},\mathbf{W})$. Then, it is

straightforward to verify that a corollary of Theorem 2 gives under the same set of assumptions:

$$\psi_J(\mathbf{v}) = \mu_{1,J}(\mathbf{v}) - \mu_{0,J}(\mathbf{v})$$

where

$$\mu_{1,J}(\mathbf{v}) = \mathbb{E}\left\{Y|A=1, \mathbf{V}=\mathbf{v}, S_J=1\right\}$$
$$\mu_{0,J}(v) = \frac{\int ... \int \mathbb{E}\left(Y|A=0, S_J=1, \overline{\mathbf{C}}_{J-1}=\overline{\mathbf{c}}_{J-1}\right) \prod_{j=2}^{J} \pi_j\left(1, \overline{\mathbf{c}}_{j-1}\right) \prod_{j=1}^{J-1} dG_{0,j}(\mathbf{c}_j; \overline{\mathbf{c}}_{j-1}) dG_{0,0}(\mathbf{w}; \mathbf{v})}{\int ... \int \prod_{j=2}^{J} \pi_j\left(1, \overline{\mathbf{c}}_{j-1}\right) \prod_{j=1}^{J-1} dG_{0,j}(\mathbf{c}_j; \overline{\mathbf{c}}_{j-1}) dG_{0,0}(\mathbf{w}; \mathbf{v})}$$

and

$$G_0(\mathbf{w}; \mathbf{v}) = \begin{cases} F(\mathbf{w}|\mathbf{v}) \text{ if } \mathbf{W} \text{ is not empty} \\ \\ 1 \text{ if } \mathbf{W} \text{ is empty} \end{cases}$$

3.2 Weighted estimation of models of SACE

A simple weighted approach is given, that is consistent under correct models for the survival process, as well as for the exposure process. Let $\{\widehat{\pi}_j(\cdot), j=2, ...J\}$ denote an estimated model for the survival process, using a standard parametric approach; likewise, let $p(\mathbf{C}_0) = \Pr(A = 1|\mathbf{C}_0)$ denote the propensity score for exposure, and $\widehat{p}(\mathbf{C}_0)$ denotes its estimator using a standard parametric approach. Define the following estimated weights for individuals who survive until the end of follow-up:

$$\widehat{W}_S = \frac{\prod_{k=2}^{J} \widehat{\pi}_k\left(1, \overline{\mathbf{C}}_{k-1}\right)}{\prod_{k=2}^{J} \widehat{\pi}_k\left(A, \overline{\mathbf{C}}_{k-1}\right)}$$
$$\widehat{W}_A = \left[\widehat{p}\left(\mathbf{C}_0\right)^A \left\{1 - \widehat{p}\left(\mathbf{C}_0\right)\right\}^{1-A}\right]^{-1}$$

Then, let $\widehat{\psi}_J$ denote the weighted ordinary least squares estimator of the marginal effect of A on Y using only data on individuals who survived until the end of follow-up, with individual weight equal to $\widehat{W}_S \times \widehat{W}_A$. Then we have the following result:

Theorem 3 *Suppose that the assumptions of Theorem 2 hold, and that* $\{\widehat{\pi}_j(\cdot), j = 2, ...J\}$ *and* $\widehat{P}(\cdot)$ *are consistent, then* $\widehat{\psi}_J$ *is consistent for* ψ_J.

The theorem states that ψ_J may be estimated consistently, by applying the weights $\widehat{W}_S \times \widehat{W}_A$ in weighted least-squares estimation of a standard linear regression of Y on A among individuals alive at the end of follow-up. Furthermore, the estimator $\widehat{\psi}_J$ is asymptotically normal under standard regularity conditions. The weights component given by $\widehat{W}_A$ corresponds to standard inverse-probability-of-treatment weighting a well-known propensity score technique to control for confounding [23,24]. Intuitively, treatment weights create possibly fractional copies of each individual with complete follow-up, such that in the weighted sample, $\mathbf{C}_0$ no longer predicts A and therefore is not a confounder. The other component of the weights $\widehat{W}_S$ corrects for selective survival of unexposed individuals. Intuitively, monotonicity of the effects of exposure on survival implies that unexposed survivors may be over-represented relative to the exposed, and thus if $\mathbf{C}_0$ were empty so that $\widehat{W}_A$ could be set to 1, then since $0 < W_S = \prod_{k=2}^{j} \pi_k\left(1, \overline{\mathbf{C}}_{k-1}\right) / \prod_{k=2}^{j} \pi_k\left(A, \overline{\mathbf{C}}_{k-1}\right) \leq 1$, we would have that the survival weight essentially adjusts the contribution of unexposed survivors downwards, and does so continuously as a function of $\overline{\mathbf{C}}_J$.

While the Theorem states the result for SACE measured on the additive scale, weighted estimation with weight $\widehat{W}_S \times \widehat{W}_A$ is an universal strategy for estimating SACE on a variety of scales often of scientific interest. For instance, the approach could be used to estimate SACE on the multiplicative scale, or for other choice of link function, such as logit or probit link functions. This could be achieved by simply replacing the normal equations by the appropriate set of estimating

equations one would have used in the absence of selective truncation by death and confounding. The approach could also be used for quantile regression, or to weight other standard likelihood or quasi-likelihood methods as a means to jointly account for selective survival and confounding. For instance, weighted partial likelihood could be used to estimate a Cox proportional hazards regression model, producing SACE estimates on the hazards ratio scale. This could be done by simply applying individuals weights within risk sets. Finally, suppose that instead of marginal causal effects, a conditional causal effect, say $\psi_J(\mathbf{C}_0)$ were in view. Then suppose that one were to use a parametric or semiparametric model $\mathbb{E}\left\{Y(a)|\mathbf{C}_0 = \mathbf{c}_0, S_J(a', \overline{\mathbf{C}}_{J-1}(a^*)) = 1;\ \text{for all } a', a^* \in \{0,1\}\,;\theta\right\}$ to describe the survivor average causal effect of A within levels of $\mathbf{C}_o$. Then assuming the model were correct, θ could then be estimated via a weighted approach, using only the survival component of the weight $\widehat{W}_S$, since the regression model would already account for baseline confounding by conditioning on $\mathbf{C}_0$. This strategy is in fact adopted in the data illustration of the next Section.

For inference about ψ_J or $\psi_J(\mathbf{C}_0)$, in general, one could use the nonparametric bootstrap such that the extra variation due to first stage estimation of the weights is appropriately accounted for. Alternatively, one could use a consistent estimate of the large sample variance of the weighted estimator of SACE to construct Wald-type confidence intervals; such an estimator of the large sample variance can be computed in a manner similar to the variance estimator given in Section 5.

4 A data application

We illustrate the methods developed in the previous section in an analysis of the effects of smoking on cognitive decline in an aging population subject to substantial attrition due to death and dropout for other reasons [25]. In their paper, Weuve et al [25] noted that selective attrition in this

population may introduce bias into analyses of the effects of smoking status measured at the start of follow-up on cognitive decline, mainly due to the facts that:

(1) an individual's evolving health status is likely to be a common cause for attrition and cognitive decline among survivors who do not drop out.

(2) an individual's evolving health status is likely to mediate the causal effect of smoking on cognitive decline.

To appropriately account for (1) and (2) Weuve et al used inverse-probability-of-attrition weights and examined the influence of selective attrition on the estimated association of current smoking (versus never smoking) with cognitive decline in participants of the Chicago Health and Aging Project (n=3,713), aged 65-109, who were current smokers or never-smokers, and underwent cognitive assessments up to 5 times at 3-year intervals. Only 20% of the original sample remained at the fourth follow-up, and mortality accounted for most ($\sim$70%) of the attrition. Weuve et al used separate pooled logistic regression to fit predictive models of attrition due to death or study drop-out across the follow-up waves using both baseline and time-updated data to construct inverse-probability-of-attrition weights. We refer the reader to Weuve et al for additional details on their design and analysis of the study, also see [11,22] for additional discussion. Similar to Weuve et al [25], we estimated a linear mean regression model contrasting rates of change in cognitive scores in current versus never-smokers, adjusting for the following pre-exposure confounders in the regression: age, sex, race, education, and alcohol consumption. As recommended by Tchetgen Tchetgen et al [26], the analysis assumed an independence correlation structure for the 5 serial measurements of cognitive function (coded as z-scores). Death and dropout for other reasons denoted D_j, were respectively modeled as discrete time hazard models via logistic models that included main effects for the following baseline and time-updated variables: age, race (African American vs. white), sex

(male vs. female), education (0–8 years, 9–12 years referent, 13–16 years, 17–30 years), alcohol consumption at the previous visit (none referent, up to 1 drink/d, 1 drink/d), social network score at the previous visit, cognitive activity at the previous visit, disability score at the previous visit, self-rated health at the previous visit (per unit worsening in rating), chronic cardiovascular conditions, diabetes, global cognitive score at the previous visit, and smoking status (current vs. never). A logistic model for non-death related censoring was also estimated using only baseline variables. These predictive models were combined as in Weuve et al to account for selective censoring other than death via stabilized weights [25]:

$$\widehat{W}_j^{\ddagger} = \frac{\prod_{k=2}^{j} \widehat{\Pr}\left(D_k = 0 | \mathbf{C}_0, A, S_k = 1\right)}{\prod_{k=2}^{j} \widehat{\Pr}\left(D_k = 0 | \overline{\mathbf{C}}_{k-1}, A, S_k = 1\right)}$$

An additional set of weights was estimated to account for truncation by death using the approach developed in Section 3.2

$$\widehat{W}_{S,j} = \frac{\prod_{k=2}^{j} \widehat{\pi}_k\left(1, \overline{\mathbf{C}}_{k-1}\right)}{\prod_{k=2}^{j} \widehat{\pi}_k\left(A, \overline{\mathbf{C}}_{k-1}\right)}$$

and the final weight $\widehat{W}_j^{\ddagger} \times \widehat{W}_{S,j}$ was applied at the level of observations within individuals, such that for each person wave contribution to our analysis at wave j, the weight was the products of censoring weights and survival weights

Confidence intervals were obtained via the bootstrap. In un-weighted analyses, current smokers' cognitive scores declined 0.11 standard units per decade more rapidly than never-smokers' (95% CI= -0.20 to -0.02). Weighting for attrition due to drop out or death using $\widehat{W}_j^{\ddagger} \times \widehat{W}_{S,j}$ for weight gave an estimate that was considerably larger, with smoking's estimated 10-year rate of decline compared with nonsmoking 55% larger than in the un-weighted analysis (95% CI=–0.27 to -0.07).

Under the assumptions of Theorem 2, this latter estimate may be interpreted as the survival average effect of smoking on cognitive decline conditional on pre-exposure covariates. Monotonicity in the current setting is uncontroversial, as it essentially states that smoking does not offer any survival benefits. The concordant survivorship assumption here essentially states that always survivors would remain as such, whether their history of covariates were set to what it would be as smokers, or as non-smokers. This in a sense clarifies that there can be neither a direct nor an indirect effect of smoking on survival in the survivors. Finally we should note that similar results were obtained for SACE when dropout for other reasons was simply ignored and the SACE weight $\widehat{W}_{S,j}$ was applied, suggesting that most of the selection bias due to attrition was related to death.

5 Results on double robustness and sensitivity analysis

5.1 Double robustness

Consider the simple setting of Section 2 where iid realizations are observed on $(A, \mathbf{C}_1, S, SY)$. The following result gives a doubly robust estimator of μ_0 in the three-occasion setting, that essentially combines $\widehat{\mu}_0^2$ and $\widehat{\mu}_0^3$ of Section 2.4, such that consistency is obtained under a union model where either $\widehat{\mathbb{E}}(Y|A=0, S=1, \mathbf{C}_1)$ and $d\widehat{F}(\mathbf{C}_1|A=0)$ are both consistent, or $\widehat{\Pr}(S=1|A=0, \mathbf{C}_1)$ is consistent, but all models are not necessarily consistent. To state the result, consider the following estimating function:

$$
\begin{aligned}
U(\mu_0) = (1-A)S\frac{\Pr(S=1|A=1,\mathbf{C}_1)}{\Pr(S=1|A=0,\mathbf{C}_1)}\left\{Y - \mathbb{E}\left(Y|A=0,S=1,\mathbf{C}_1\right)\right\} \\
+ A\mathbb{E}\left(Y|A=0,S=1,\mathbf{C}_1\right)\frac{dF(\mathbf{C}_1|A=0)}{dF(\mathbf{C}_1|A=1)}\left\{S - \Pr(S=1|A=1,\mathbf{C}_1)\right\} \\
+ \left\{(1-A)\mathbb{E}\left(Y|A=0,S=1,\mathbf{C}_1\right)\Pr(S=1|A=1,\mathbf{C}_1) - \mu_0\right\},
\end{aligned}
$$

and define $\widehat{U}(\mu_0)$ similarly, evaluated at $\{\widehat{\mathbb{E}}\left(Y|A,S=1,\mathbf{C}_1\right),\widehat{\Pr}(S=1|A,\mathbf{C}_1),d\widehat{F}(\mathbf{C}_1|A)\}$ instead of $\{\mathbb{E}\left(Y|A,S=1,\mathbf{C}_1\right),\Pr(S=1|A,\mathbf{C}_1),dF(\mathbf{C}_1|A=0)\}$.

Theorem 4 *Under the assumptions of Theorem 1, $\widehat{\mu}_0^{dr}$ is doubly robust and therefore converges to μ_0 and is asymptotically normal if one but not necessarily both of the following conditions hold.*

1. $\widehat{\mathbb{E}}\left(Y|A,S=1,\mathbf{C}_1\right)$ *and* $d\widehat{F}(\mathbf{C}_1|A=0)/d\widehat{F}(\mathbf{C}_1|A=1)$ *are both consistent;*

2. $\widehat{\Pr}(S=1|A,\mathbf{C}_1)$ *is consistent;*

   where $\widehat{\mu}_0^{dr}$ satisfies the estimating equation $\mathbb{P}_n\left\{\widehat{U}(\widehat{\mu}_0^{dr})\right\}=0$. Furthermore, at the intersection submodel where all estimators are consistent, $\widehat{\mu}_0^{dr}$ is semiparametric efficient in the nonparametric model where no model assumption is made, at the intersection submodel where both of the above conditions 1. and 2. hold;

The theorem gives an estimator of μ_0 that is doubly robust and that is semiparametric efficient in the nonparametric model where no modeling assumption is made, at the intersection submodel where all working models are correct. This last property is sometimes called semiparametric local efficiency. At the intersection submodel, the asymptotic variance of $\widehat{\mu}_0^{dr}$ can be estimated by the simple expression $\mathbb{P}_n\left\{\widehat{U}(\widehat{\mu}_0^{dr})^2\right\}^{-1}$. Interestingly, one may note that, this expression is invariant to the choice of working models and associated estimators. This property does not apply outside of the intersection submodel, nonetheless, it remains possible to estimate the asymptotic variance of $\widehat{\mu}_0^{dr}$ outside the intersection submodel. To do so, let $\widehat{\gamma}_Y,\widehat{\gamma}_{\mathbf{C}_1}$ and $\widehat{\gamma}_S$ denote the estimates of $\gamma_Y,\gamma_{\mathbf{C}_1}$ and γ_S, the parameters indexing models for $\mathbb{E}\left(Y|A,S=1,\mathbf{C}_1\right)$, $F(\mathbf{C}_1|A=0)$ and $\Pr(S=1|A,\mathbf{C}_1)$ respectively. Suppose that such estimates are obtained by solving a set of score equations with respective scores $\mathbf{M}_Y\left(\gamma_Y\right),\mathbf{M}_{\mathbf{C}_1}\left(\gamma_{\mathbf{C}_1}\right)$ and $\mathbf{M}_S\left(\gamma_S\right)$. Let $\mathbf{M}\left(\gamma_Y,\gamma_{\mathbf{C}_1},\gamma_S\right)=\left(\mathbf{M}_Y^T\left(\gamma_Y\right),\mathbf{M}_{\mathbf{C}_1}^T\left(\gamma_{\mathbf{C}_1}\right),\mathbf{M}_S^T\left(\gamma_S\right)\right)^T$, and define $U(\mu_0,\gamma_Y,\gamma_{\mathbf{C}_1},\gamma_S)$ to equal $U(\mu_0)$

under the parametric model, such that $\widehat{U}(\mu_0) = U(\mu_0, \widehat{\gamma}_Y, \widehat{\gamma}_{\mathbf{C}_1}, \widehat{\gamma}_S)$. Then a standard Taylor series expansion can be used to show that the large sample variance of $\widehat{\mu}_0^{dr}$ is consistently estimated by $\widehat{\mathbf{\Gamma}}^{-1}\widehat{\mathbf{\Omega}}\,\widehat{\mathbf{\Gamma}}^{-1}$, where

$$
\begin{aligned}
\widehat{\mathbf{\Gamma}}^{-1} &= \mathbb{P}_n\left(\frac{\partial U(\mu_0, \widehat{\gamma}_Y, \widehat{\gamma}_{\mathbf{C}_1}, \widehat{\gamma}_S)}{\partial \mu_0}\Big|_{\widehat{\mu}_0^{dr}}\right) \\
\widehat{\mathbf{\Omega}} &= \mathbb{P}_n\left(\widehat{\mathbf{L}}\widehat{\mathbf{L}}^T\right) \\
\widehat{\mathbf{L}} &= U(\widehat{\mu}_0^{dr}, \widehat{\gamma}_Y, \widehat{\gamma}_{\mathbf{C}_1}, \widehat{\gamma}_S) - \mathbb{P}_n\left(\frac{\partial U(\widehat{\mu}_0^{dr}, \gamma_Y, \gamma_{\mathbf{C}_1}, \gamma_S)}{\partial\left(\gamma_Y^T, \gamma_{\mathbf{C}_1}^T, \gamma_S^T\right)^T}\Big|_{\left(\widehat{\gamma}_Y^T, \widehat{\gamma}_{\mathbf{C}_1}^T, \widehat{\gamma}_S^T\right)^T}\right) \\
&\quad \times \mathbb{P}_n\left(\frac{\partial \mathbf{M}(\gamma_Y, \gamma_{\mathbf{C}_1}, \gamma_S)}{\partial\left(\gamma_Y, \gamma_{\mathbf{C}_1}, \gamma_S\right)^t}\Big|_{\left(\widehat{\gamma}_Y^T, \widehat{\gamma}_{\mathbf{C}_1}^T, \widehat{\gamma}_S^T\right)^T}\right)^{-1} \mathbf{M}\left(\widehat{\gamma}_Y, \widehat{\gamma}_{\mathbf{C}_1}, \widehat{\gamma}_S\right)
\end{aligned}
$$

5.2 Sensitivity analysis

A key assumption for identification of SACE has been that there is no unmeasured common cause of survival and the outcome Y, as encoded say in the causal diagram of Figure 1, and its associated NPSEM $(1)-(4)$. In the current section, a sensitivity analysis technique is developed to assess the extent to which a violation of the assumption might affect results. Unlike previous sensitivity analysis techniques for truncation by death and related contexts [7,8,12,13], the proposed sensitivity analysis technique makes explicit use of post-exposure covariates and therefore extends previous methods to the current more general longitudinal context. We begin by describing the approach in the simple setting from Section 2, of a 3-occasion study. Define the selection bias function:

$$
\begin{aligned}
t(\mathbf{c}_1) = &\ \mathbb{E}\left\{Y(a=0) | A=0, \mathbf{C}_1(a=0) = \mathbf{c}_1, S(a=0) = S(a=1, \mathbf{C}_1(a=0) = \mathbf{c}_1) = 1\right\} \\
&- \mathbb{E}\left\{Y(a=0) | A=0, \mathbf{C}_1(a=0) = \mathbf{c}_1, S(a=0) = 1, S(a=1, \mathbf{C}_1(a=0) = \mathbf{c}_1) = 0\right\}
\end{aligned}
$$

We have that $t(\cdot) = 0$ under the independence assumptions encoded in the NPSEM $(1) - (4)$, however if there were an unmeasured common cause of S and Y, such that ε_Y and ε_S were no longer independent, then we would expect that $t(\mathbf{c}_1) \neq 0$ for some value of $\mathbf{c}_1$, even though all other independencies of the NPSEM were to continue to hold. Thus, we propose to recover inferences about SACE by assuming that the selection bias function $t(\mathbf{c}_1)$ is known, that encodes the magnitude and direction of the unmeasured common cause of S and Y. To motivate the proposed approach, suppose for the moment that $\pi(a, \mathbf{C}_1) = \Pr(S|a, \mathbf{C}_1)$ is known, then we show in the appendix that:

$$\begin{aligned}
&\mathbb{E}\left\{Y(a=0)|A=0, \mathbf{C}_1(a=0)=\mathbf{c}_1, S(a=0)=S(a=1, \mathbf{C}_1(a=0)=\mathbf{c}_1)=1\right\} \qquad (16)\\
&= \mathbb{E}\left\{Y(a=0)|A=0, \mathbf{C}_1(a=0)=\mathbf{c}_1, S(a=0)=1\right\} + t(\mathbf{c}_1) \times \left\{1 - \frac{\pi(1, \mathbf{c}_1)}{\pi(0, \mathbf{c}_1)}\right\}\\
&= \mathbb{E}\left\{Y|A=0, \mathbf{C}_1=\mathbf{c}_1, S=1\right\} + t(\mathbf{c}_1) \times \left\{1 - \frac{\pi(1, \mathbf{c}_1)}{\pi(0, \mathbf{c}_1)}\right\}
\end{aligned}$$

therefore, knowing $t(\mathbf{c}_1)$ allows one to recover the average potential outcome when unexposed in the principal strata of survivors $\{S(a=0) = S(a=1, \mathbf{C}_1(a=0) = \mathbf{c}_1) = 1\}$, by adjusting the average observed outcome in the unexposed that survived, using the above expression. The above result can then be combined with the representation of $\mu_0 = \mathbb{E}\left\{Y(a=0)|\ S(a, \mathbf{C}_1(a')) = 1; a, a' = 0, 1\right\}$ given by equation (10) of Section 2, to obtain the following modified estimator:

$$\widehat{\mu}_0(t) = \frac{\mathbb{P}_n\left\{(1-A)\frac{\widehat{\pi}(1,\mathbf{C}_1)}{\widehat{\pi}(0,\mathbf{C}_1)}\left[Y + t(\mathbf{C}_1) \times \left\{1 - \frac{\widehat{\pi}(1,\mathbf{C}_1)}{\widehat{\pi}(0,\mathbf{C}_1)}\right\}\right] S\right\}}{\mathbb{P}_n\left\{(1-A)S\frac{\widehat{\pi}(1,\mathbf{C}_1)}{\widehat{\pi}(0,\mathbf{C}_1)}\right\}}$$

A formal sensitivity analysis can be obtained by repeating this process and reporting inferences about $\mu_1 - \mu_0$ using $\widehat{\mu}_1 - \widehat{\mu}_0(t)$ and a corresponding confidence interval for each choice of $t(\cdot)$ say in a finite set of user–specified functions $\mathcal{T} = \{\ t_\lambda(\cdot) : \lambda\}$ indexed by a finite dimensional parameter

λ with $t_0(\cdot) \in \mathcal{T}$ corresponding to the assumption of no unmeasured common cause of Y and S, i.e. $t_0(\cdot) \equiv 0$.

As is shown next, the above approach readily extends to the more general context of a longitudinal study with $J > 3$ occasions described in Section 3. Define the selection bias function:

$$t_J(\overline{\mathbf{c}}_{J-1}) = \mathbb{E}\left\{Y(a=0)|A=0, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}, S_J(a=0) = S_J(a=1, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}) = 1\right\}$$
$$- \mathbb{E}\left\{Y(a=0)|A=0, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}, S_J(a=0) = 1, S_J(a=1, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}) = 0\right\}$$

We have that, similar to the 3-occasion scenario, $t_J(\cdot) = 0$ under the independence assumptions encoded in the NPSEM $(11) - (14)$, however if there were an unmeasured common cause of the survival process and Y among indiviuduals that survive follow-up, such that ε_Y and $\{\varepsilon_{S_j} : j\}$ were no longer independent, then we would expect that $t_J(\overline{\mathbf{c}}_{J-1}) \neq 0$ for some value of $\overline{\mathbf{c}}_{J-1}$, even though all other independencies of the NPSEM were to continue to hold.Then, similar to the three occasion derivation, one obtains the following relation which is derived in the appendix:

$$\begin{aligned}
&\mathbb{E}\left\{Y(a=0)|A=0, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}, S_J(a=0) = S_J(a=1, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}) = 1\right\} \quad (17)\\
&= \mathbb{E}\left\{Y(a=0)|A=0, \overline{\mathbf{C}}_{J-1}(a=0) = \overline{\mathbf{c}}_{J-1}, S_J(a=0) = 1\right\} + t_J(\overline{\mathbf{c}}_{J-1}) \times \left\{1 - \frac{\prod_{j=2}^{J} \pi_j\left(1, \overline{\mathbf{c}}_{j-1}\right)}{\prod_{j=2}^{J} \pi_j\left(0, \overline{\mathbf{c}}_{j-1}\right)}\right\}\\
&= \mathbb{E}\left\{Y|A=0, \overline{\mathbf{C}}_{J-1} = \overline{\mathbf{c}}_{J-1}, S_J = 1\right\} + t_J(\overline{\mathbf{c}}_{J-1}) \times \left\{1 - \frac{\prod_{j=2}^{J} \pi_j\left(1, \overline{\mathbf{c}}_{j-1}\right)}{\prod_{j=2}^{J} \pi_j\left(0, \overline{\mathbf{c}}_{j-1}\right)}\right\}
\end{aligned}$$

The above result can then be combined with the representation of $\mu_{0,J}$ from Section 3, to obtain the following modified expression, that incorporates the selection bias function:

$$\frac{\mathbb{E}\left\{(1-A)W_S W_A\left[Y + t_J(\overline{\mathbf{c}}_{J-1}) \times (1 - W_S)\right] S_J\right\}}{\mathbb{E}\left\{(1-A)S_J W_S W_A\right\}}$$

where recall that

$$W_S = \frac{\prod_{k=2}^{J} \pi_k \left(1, \overline{\mathbf{C}}_{k-1}\right)}{\prod_{k=2}^{J} \pi_k \left(A, \overline{\mathbf{C}}_{k-1}\right)}$$
$$W_A = \left[p\left(\mathbf{C}_0\right)^A \left\{1 - p\left(\mathbf{C}_0\right)\right\}^{1-A}\right]^{-1}$$

which in turn can be used to obtain a consistent estimator. A sensitivity analysis then simply proceeds similar to the three-occasion setting described above.

6 Survivor Marginal Structural Models

It is now well known that within the context of a time-varying exposure with time-varying confounding, standard confounding adjustment techniques, such as stratification or standard regression analysis in general cannot appropriately account for time varying-confounding and therefore can be biased for the joint causal effects of the exposure, even under the causal null hypothesis of no exposure effect over time. In fact, the standard use of regression models to estimate the causal effect of a time varying exposure, can be biased even in the absence of unmeasured confounders whether or not one adjusts further for the past history of measured covariates in the analysis, when (a) there exists a time-dependent risk factor for the outcome that also predicts subsequent exposure, and (b) past exposure history predicts subsequent risk factor level. The reason is, when both conditions (a) and (b) hold, an analysis that does not adjust for past covariates is biased due to uncontrolled confounding, yet an analysis that includes current covariates is also biased as it adjusts for a variable affected by past exposure.

Marginal Structural Models (MSMs) were introduced by Robins [27] to estimate the joint causal effect of a time-dependent exposure in the presence of time-dependent confounders that

are themselves intermediate variables, affected by previous exposure. MSMs were proposed as an alternative approach to the semiparametric g-computation algorithm estimator [1] and to g-estimation of structural nested models (SNMs) [27]. Robins [27] and subsequently Hernan et al [28] described inverse probability-of-treatment-weighted (IPTW) estimation of MSMs, a method which in contrast to standard methods, provides consistent estimates of causal effects when unmeasured confounding, model misspecification and truncation by death are absent. We extend the results of previous sections to the context of MSMs.

First, we redefine the NPSEM to allow for a time-updated exposure, and we assume no other form of loss to follow-up is present. Let $A_0 = 0$, such that individuals are assumed to be unexposed at start of follow-up, and let $\mathbf{C}_{-1} = 0$; then, for $j = 0, ..., J$:

$$\mathbf{C}_j = \begin{cases} \mathbf{g}_{\mathbf{C}_j}(\overline{A}_j, \overline{\mathbf{C}}_{j-1}, \varepsilon_{\mathbf{C}_j}) & \text{if } S_j = 1; \\ \text{undefined} & \text{if } S_j = 0. \end{cases} \tag{18}$$

$$S_{j+1} = \begin{cases} g_{S_{j+1}}\left(\overline{A}_j, \overline{\mathbf{C}}_j, \varepsilon_{S_{j+1}}\right) & \text{if } S_j = 1; \\ 0 & \text{if } S_j = 0; \end{cases} \tag{19}$$

$$A_{j+1} = \begin{cases} g_{A_{j+1}}\left(\overline{A}_j, \overline{\mathbf{C}}_j, \varepsilon_{A_{j+1}}\right) & \text{if } S_{j+1} = 1; \\ \text{undefined} & \text{if } S_{j+1} = 0; \end{cases} \tag{20}$$

Let $Y = \mathbf{C}_J$ denote the outcome. We assume that

$$\left\{\varepsilon_{A_j} : j \geq 1\right\} \perp\!\!\!\perp \left\{\varepsilon_{s_j} : j \geq 1\right\},$$

and we also assume that:

$$\left\{\varepsilon_{A_j}, \varepsilon_{s_j} : j \geq 1\right\} \perp\!\!\!\perp \left\{\varepsilon_{\mathbf{C}_j} : j \geq 0\right\}$$

However, as before $\varepsilon_{\mathbf{C}_j}$ and $\varepsilon_{\mathbf{C}_{j'}}$ may be dependent,and ε_{s_j} and $\varepsilon_{s_{j'}}$ may be dependent, $j \neq j'$. The NPSEM in the above display and the associated error independencies essentially states that $\overline{\mathbf{C}}_{j-1}$ is sufficiently enriched so that $(\overline{A}_{j-1}, \overline{\mathbf{C}}_{j-1})$ accounts for potential association between S_j and $\mathbf{C}_j$ and likewise so that $(\overline{A}_{j-1}, \overline{\mathbf{C}}_{j-1})$ accounts for confounding of the causal effects of A_j.

To account for truncation by death, consider the average potential outcome in the survivors:

$$\mu_J(\overline{a})$$
$$= \mathbb{E}\left\{Y(\overline{a})|S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{a}^*))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{a}^*))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1;\ \text{for all } \overline{a}^* \in \{0,1\}^J\right\}$$

The conditioning event of the above expectation would be satisfied if an individual would survive irrespective of exposure history, including under certain cross-world situations where the covariate history behaves as if under an exposure history that possibly conflicts with that influencing the outcome. Thus, SMSMs give a natural generalization of standard MSMs to account for truncation by death. In the special case where $S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{a}^*))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1 \Rightarrow S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{a}^*))S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1$ almost surely, then $\mu_J(\overline{a})$ simplifies and may be written

$$\mathbb{E}\left\{Y(\overline{a})|S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{a}^*)) = S_J(\overline{a}^*) = 1;\ \overline{a}^* \in \{0,1\}^J\right\}$$

which extends the standard definition of SACE to time-updated exposure settings.

Identification of $\mu_J(\overline{a})$ requires a modification of the Monotonicity and Concordant Survivorship assumptions:

Sequential Monotonicity Assumption for Time-dependent Exposure:*For any treatment history*

$\overline{a}_{j-1} \in \{0,1\}^{J-1}$, *if*

$$S_{j-1}(\overline{a}_{j-2}, \overline{\mathbf{C}}_{j-2}(\overline{a}_{j-3}))S_{j-1}(\overline{0}_{j-2}, \overline{\mathbf{C}}_{j-2}(\overline{a}_{j-3})) = 1 \text{ almost surely}$$

then

$$S_j(\overline{0}_{j-1}, \overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2})) \leq S_j(\overline{a}_{j-1}, \overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2})) \text{ almost surely}$$

where $S_0(\cdot,\cdot) = 1$ *almost surely; and if*

$$S_{j-1}(\overline{a}_{j-2}, \overline{\mathbf{C}}_{j-2}(\overline{0}_{j-3}))S_{j-1}(\overline{0}_{j-2}, \overline{\mathbf{C}}_{j-2}(\overline{0}_{j-3})) = 1 \text{ almost surely}$$

then

$$S_j(\overline{0}_{j-1}, \overline{\mathbf{C}}_{j-1}(0)) \leq S_j(\overline{a}_{j-1}, \overline{\mathbf{C}}_{j-1}(\overline{0}_{j-2})) \text{ almost surely}$$

<u>*Concordant Survivorship Assumption for Time-dependent Exposure* :</u>

$$\text{if either } S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{a}^*))S_J(\overline{0}_{J-1}, \overline{\mathbf{C}}_{J-1}(\overline{a}^*)) = 1 \text{ or } S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}^*))S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1$$

almost surely, for some exposure history $\overline{a}^*$, then

$$S_J(\overline{a}^{**}, \overline{\mathbf{C}}_{J-1}(\overline{a}^{**}))S_J(\overline{0}_{J-1}, \overline{\mathbf{C}}_{J-1}(\overline{a}^{**})) = 1$$

$$\text{and } S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))S_J(\overline{a}^{**}, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1 \text{ for all } \overline{a}^{**}, \text{ almost surely.}$$

We should note that the Sequential Monotonicity Assumption essentially states that receiving a dose of exposure can never be harmful for survival relative to remaining unexposed over time, and

therefore in contrast with previous sections where exposure was taken to be smoking history and therefore harmful for survival, here exposure is imagined to be a protective treatment with respect to survival, such as say highly active antiretroviral therapy for HIV patients [21]. Specifically, the condition states that for a person that would survive up to time $j-1$ if either untreated or with treatment history $\overline{a}$, in the hypothetical situation where his covariate history behaves as if his treatment history were set to $\overline{a}$, and the person were to survive at time j when untreated and with covariate history as if treatment followed regime $\overline{a}$, then the person would also survive at time j, with similar covariate history, if his treatment history were set to $\overline{a}$.

The Concordant Survivorship Assumption essentially states that a person that would survive under a given treatment history $\overline{a}^*$, as well as if he were never exposed, in the hypothetical situation where his covariate history behaves as if his exposure history were set to $\overline{a}^*$, then he would also survive under any other treatment history $\overline{a}^{**}$, and would likewis survive if he were never exposed, in the hypothetical situation where his covariate history behaves as if his exposure history were set to $\overline{a}^{**}$. A similar assumption is made for an individual for whom $S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}^*))S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1$ for some $\overline{a}^*$. Throughout, we make the following positivity assumptions that

$$\prod_{k=2}^{J} \pi_k\left(\overline{0}_{k-1}, \overline{\mathbf{C}}_{k-1}\right) / \prod_{k=2}^{J} \pi_k\left(\overline{a}_{k-1}, \overline{\mathbf{C}}_{k-1}\right) < \infty \text{ almost surely,}$$

and if

$$f(\overline{A}_j = \overline{a}_j, \overline{\mathbf{C}}_j = \overline{\mathbf{c}}_j, S_j = 1) > 0 \text{ then } f(A_{j+1} = a_{j+1} | \overline{A}_j = \overline{a}_j, \overline{\mathbf{C}}_j = \overline{\mathbf{c}}_j, S_j = 1) > 0 \text{ almost surely,}$$

Then we have the following result:

Theorem 5 *Under the NPSEM given by equations* $(11)-(14)$, *the Sequential Monotonicity As-*

sumption for time-dependent exposure, the Concordant Survivorship Assumption for time-dependent exposure and the positivity assumptions, we have that $\mu_J(\overline{a})$ is nonparametricaly identified and is given by

$$\mu_J(\overline{a}) = \frac{\int ... \int \mathbb{E}\left(Y|\overline{A} = \overline{a}, S_J = 1, \overline{\mathbf{C}}_{J-1} = \overline{\mathbf{c}}_{J-1}\right) \prod_{j=2}^{J} \pi_j\left(\overline{0}_{j-1}, \overline{\mathbf{c}}_{j-1}\right) \prod_{j=0}^{J-1} dG_j(\mathbf{c}_j; \overline{a}_{j-1}, \overline{\mathbf{c}}_{j-1})}{\int ... \int \prod_{j=2}^{J} \pi_j\left(\overline{0}_{j-1}, \overline{\mathbf{c}}_{j-1}\right) \prod_{j=0}^{J-1} dG_j(\mathbf{c}_j; \overline{a}_{j-1}, \overline{\mathbf{c}}_{j-1})}$$

where

$$\pi_j(\overline{a}_{j-1}, \overline{\mathbf{c}}_{j-1}) = \Pr(S_j = 1|\overline{A}_{j-1} = \overline{a}_{j-1}, \overline{\mathbf{C}}_{j-1} = \overline{\mathbf{c}}_{j-1}, S_{j-1} = 1), j = 2, ...J;$$

$$G_j(\mathbf{c}_j; \overline{a}_j, \overline{\mathbf{c}}_{j-1}) = F(\mathbf{c}_j|\overline{A}_j = \overline{a}_j, \overline{\mathbf{C}}_{j-1} = \overline{\mathbf{c}}_{j-1}, S_j = 1),\ \ j = 0, ..., J-1;$$

For inference about $\mu_J(\overline{a})$, in practice, one could proceed as in Hernan et al [21] and one could specify a model $\mu_J(\overline{a}; \lambda)$ indexed by an unknown parameter λ. We shall refer to such a model as a Survivor Marginal Structural Model (SMSM), since it is an MSM for individuals that would survive under any treatment history, including under certain cross-world situations where the covariate history behaves as if under a possibly conflicting exposure history to that influencing the outcome. For instance, consider the simple linear SMSM:

$$\mu_J(\overline{a}; \lambda) = (1, cum(\overline{a}))\lambda$$

where $cum(\overline{a})) = \sum_{j=1}^{J} a_j$. Then, as in the weighted least squares approach developed in Section 3.2, one can likewise show that a consistent weighted least squares estimator of the SMSM parameter λ can be obtained by using the following modified weights $\widehat{W}_S^{\#} \times \widehat{W}_A^{\#}$ to jointly account for time-

dependent exposure, time-dependent confounding, and death related attrition:

$$\widehat{W}_S^{\#} = \frac{\prod_{j=2}^{J} \widehat{\pi}_j \left(\overline{0}_{j-1}, \overline{\mathbf{C}}_{j-1}\right)}{\prod_{j=1}^{J} \widehat{\pi}_j \left(\overline{A}_{j-1}, \overline{\mathbf{C}}_{j-1}\right)}$$

$$\widehat{W}_A^{\#} = \prod_{j=1}^{J} \left[\widehat{p}_j \left(\overline{A}_{j-1}, \overline{\mathbf{C}}_{J-1}\right)^{A_j} \left\{1 - \widehat{p}_j \left(\overline{A}_{j-1}, \overline{\mathbf{C}}_{J-1}\right)\right\}^{1-A_j}\right]^{-1}$$

where $\widehat{\pi}_j(\cdot,\cdot)$ is a consistent estimator of π_j and $\widehat{p}_j\left(\overline{A}_{j-1}, \overline{\mathbf{C}}_{J-1}\right)$ is a consistent estimator of $p_j\left(\overline{A}_{j-1}, \overline{\mathbf{C}}_{J-1}\right) = \Pr(A_j|\overline{A}_{j-1}, \overline{\mathbf{C}}_{J-1})$. For inference, one may use the nonparametric bootstrap to compute standard errors and corresponding confidence intervals.

7 Discussion

A general approach is proposed in this paper for identification and estimation of causal effects when the outcome in view is subject to truncation by death. The proposed approach is shown to equally apply in the context of a point treatment or exposure, but also if joint effects of a time-updated exposure are in view. A simple weighted approach is described for estimation, that easily scales with follow-up of increasing length and applies irrespective of whether the exposure is time-updated or occurs at a single point in time. Doubly robust estimation is shown to be possible in the simple context of a three-occasion follow-up study with point exposure. However, it is not clear that similar doubly robust estimation is possible in the more general context of a longitudinal study of arbitrary length, however, such generalizations are of definite interest and deserve further investigation. Also, a sensitivity analysis technique is developed for the general framework of a longitudinal study of arbitrary length, that can be used to evaluate the extent to which a violation of the assumption that observed post-exposure covariates fully explain the association between the outcome and attrition due to death, may bias the results.

A key assumption for identification is best illustrated in the simple setting of Figure 1, that encodes an assumption that there can be no unmeasured common cause of $\mathbf{C}_1$ and S, which may be difficult to ensure in certain settings. However, if such confounders were observed, simply adding them to $\mathbf{C}_1$ would allow for the methods to continue to apply. Furthermore, one should note that causes of death that do not also cause the outcome in those that survive, are not strictly required to be in $\mathbf{C}_1$ which makes the assumption somewhat less restrictive, particularly in settings where $\mathbf{C}_1$ only contains relatively few important causes of death. Although, an appropriate sensitivity analysis technique for the assumption of no unmeasured common cause of $\mathbf{C}_1$ and S needs to be developed and is a current subject of active research.

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Appendix

Proof of Theorem 1: We can write

$$\psi = \mathbb{E}\left\{Y(a=1) - Y(a=0) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\}$$

$$= \mathbb{E}\left\{Y(a=1) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\}$$

$$- \mathbb{E}\left\{\ Y(a=0) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\}$$

Then, note that by the Concordant Survivorship Assumption

$$\mathbb{E}\left\{Y(a=1) | S(a=0, \mathbf{C}_1(a^*)) = S(a=1, \mathbf{C}_1(a^*)) = 1,\ a^* = 0, 1\right\}$$

$$= \mathbb{E}\left\{Y(a=1) | S(a=0, \mathbf{C}_1(1)) = S(a=1, \mathbf{C}_1(1)) = 1\right\}$$

$$= \frac{\mathbb{E}\left\{Y(a=1) S(a=0, \mathbf{C}_1(1)) S(a=1, \mathbf{C}_1(1))\right\}}{\mathbb{E}\left\{S(a=0, \mathbf{C}_1(1)) S(a=1, \mathbf{C}_1(1))\right\}}$$

and by the Monotonicity Assumption

$$\mathbb{E}\left\{Y(a=1) S(a=0, \mathbf{C}_1(1)) S(a=1, \mathbf{C}_1(1))\right\}$$

$$= \mathbb{E}\left\{Y(a=1) S(a=1, \mathbf{C}_1(1))\right\}$$

$$= \int \mathbb{E}\left\{Y(a=1) | S(a=1, \mathbf{C}_1(1) = \mathbf{c}_1) = 1, \mathbf{C}_1(1) = \mathbf{c}_1)\right\} \Pr(S(a=1, \mathbf{C}_1(1) = \mathbf{c}_1) = 1 | \mathbf{C}_1(1) = \mathbf{c}_1) dF_{\mathbf{C}_1(1)}(\mathbf{c}_1$$

$$= \int \mathbb{E}\left\{Y | A=1, S=1, \mathbf{C}_1 = \mathbf{c}_1)\right\} \Pr(S=1 | \mathbf{C}_1 = \mathbf{c}_1, A=1) dF_{\mathbf{C}_1 | A=1}(\mathbf{c}_1 | A=1)$$

by the independence assumptions associated with the NPSEM; and similarly

$$\mathbb{E}\left\{S(a=0,\mathbf{C}_1(1))S(a=1,\mathbf{C}_1(1))\right\}$$
$$=\int \Pr(S=1|\mathbf{C}_1=\mathbf{c}_1,A=1)dF_{\mathbf{C}_1|A=1}(\mathbf{c}_1|A=1)$$

and therefore

$$\mathbb{E}\left\{Y(a=1)|S(a=0,\mathbf{C}_1(a^*))=S(a=1,\mathbf{C}_1(a^*))=1,\ a^*=0,1\right\}$$
$$=\mathbb{E}\left\{Y|A=1,S=1)\right\}$$

Next consider

$$\mathbb{E}\left\{Y(a=0)|S(a=0,\mathbf{C}_1(a^*))=S(a=1,\mathbf{C}_1(a^*))=1,\ a^*=0,1\right\}$$
$$=\mathbb{E}\left\{Y(a=0)|S(a=0,\mathbf{C}_1(0))=S(a=1,\mathbf{C}_1(0))=1\right\}$$
$$=\frac{\mathbb{E}\left\{Y(a=0)S(a=0,\mathbf{C}_1(0))S(a=1,\mathbf{C}_1(0))\right\}}{\mathbb{E}\left\{S(a=0,\mathbf{C}_1(0))S(a=1,\mathbf{C}_1(0))\right\}}$$

Note that

$$\mathbb{E}\left\{Y(a=0)S(a=0,\mathbf{C}_1(0))S(a=1,\mathbf{C}_1(0))\right\}$$
$$=\int \mathbb{E}\left\{Y(a=0)|S(a=0,\mathbf{C}_1(0)=\mathbf{c}_1)=S(a=1,\mathbf{C}_1(0)=\mathbf{c}_1)=1,\mathbf{C}_1(0)=\mathbf{c}_1)\right\}$$
$$\times \Pr(S(a=1,\mathbf{C}_1(0)=\mathbf{c}_1)S(a=0,\mathbf{C}_1(0)=\mathbf{c}_1)=1|\mathbf{C}_1(0)=\mathbf{c}_1)dF_{\mathbf{C}_1(0)}(\mathbf{c}_1)$$
$$=\int \mathbb{E}\left\{Y(a=0)|S(a=0,\mathbf{c}_1)=1,\mathbf{C}_1(0)=\mathbf{c}_1)\right\}$$
$$\times \Pr(S(a=1,\mathbf{c}_1)=1|A=1,\mathbf{C}_1(0)=c_1)dF_{\mathbf{C}_1|A}(\mathbf{c}_1|A=0)$$ (monotonicity & NPSEM independence)

$$=\int \mathbb{E}\left\{Y(a=0)|S(a=0,\mathbf{c}_1)=1,\mathbf{C}_1(0)=\mathbf{c}_1)\right\}$$

$\times \Pr(S(a=1,\mathbf{c}_1)=1|A=1,\mathbf{C}_1(1)=\mathbf{c}_1)dF_{\mathbf{C}_1|A}(\mathbf{c}_1|A=0)$ (NPSEM independence)

$=\int \mathbb{E}\left\{Y|A=0,S=1,\mathbf{C}_1=\mathbf{c}_1)\right\}$ (NPSEM independence)

$\times \Pr(S=1|A=1,\mathbf{C}_1=\mathbf{c}_1)dF_{\mathbf{C}_1|A}(\mathbf{c}_1|A=0)$.

Likewise,

$\mathbb{E}\left\{S(a=0,\mathbf{C}_1(0))S(a=1,\mathbf{C}_1(0))\right\}$

$=\int \Pr(S=1|A=1,\mathbf{C}_1=\mathbf{c}_1)dF_{\mathbf{C}_1|A}(\mathbf{c}_1|A=0)$, which proves the theorem.

□

Proof of Theorem 2: Similarly to the proof of Theorem 1, note that

$$\begin{aligned}\mu_{1,J} &= \mathbb{E}\left\{Y(a=1)|S_J(a,\overline{\mathbf{C}}_{J-1}(a^*))=1;\ a,a^*\in\{0,1\}\right\}\\ &= \frac{\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))S_J(0,\overline{\mathbf{C}}_{J-1}(1))\ \right\}}{\mathbb{E}\left\{S_J(1,\overline{\mathbf{C}}_{J-1}(1))S_J(0,\overline{\mathbf{C}}_{J-1}(1))\ \right\}}\end{aligned}$$

by the Concordant Survivorship Assumption, furthermore, by the Sequential Monotonicity Assumption:

$$\begin{aligned}&\frac{\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))S_J(0,\overline{\mathbf{C}}_{J-1}(1))\ \right\}}{\mathbb{E}\left\{S_J(1,\overline{\mathbf{C}}_{J-1}(1))S_J(0,\overline{\mathbf{C}}_{J-1}(1))\ \right\}}\\ &= \frac{\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))\right\}}{\mathbb{E}\left\{S_J(1,\overline{\mathbf{C}}_{J-1}(1))\right\}}\end{aligned}$$

Then, note that

$$
\begin{aligned}
&\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))\right\} \\
&= \mathbb{E}\left[\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))|\overline{\mathbf{C}}_1\right\}\right] \\
&= \mathbb{E}\left[\mathbb{E}\left\{\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))|S_2(1,\overline{\mathbf{C}}_{J-1}(1))=1,\overline{\mathbf{C}}_1\right\}\Pr\left(S_2(1,\overline{\mathbf{C}}_{J-1}(1))=1|\overline{\mathbf{C}}_1\right)|\overline{\mathbf{C}}_1\right\}\right] \\
&\vdots \\
&= \int ... \int \mathbb{E}\left\{Y(a=1,\overline{\mathbf{c}}_{J-1}(1))|S_J(1,\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_{J-1}(1)=\overline{\mathbf{c}}_{J-1}\right\} \\
&\times \prod_{j=2}^{J}\Pr\left(S_j(1,\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(1)=\overline{\mathbf{c}}_{j-1},S_{j-1}(1,\overline{\mathbf{c}}_{j-2})=1\right) \\
&\times \prod_{j=0}^{J-1} dF_{\mathbf{C}_j(1,\overline{\mathbf{c}}_{j-1})|\overline{\mathbf{C}}_{j-1}(1),S_j(1,\overline{\mathbf{C}}_{j-1}(1))=1}\left(\mathbf{c}_j|S_j(1,\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(1)=\overline{\mathbf{c}}_{j-1}\right) \\
&= \int ... \int \mathbb{E}\left\{Y(a=1,\overline{\mathbf{c}}_{J-1}(1))|A=1,S_J(1,\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_{J-1}(1)=\overline{\mathbf{c}}_{J-1}\right\} \\
&\prod_{j=2}^{J}\Pr\left(S_j(1,\overline{\mathbf{c}}_{j-1})=1|A=1,\overline{\mathbf{C}}_{j-1}(1)=\overline{\mathbf{c}}_{j-1},S_{j-1}(1,\overline{\mathbf{c}}_{j-2})=1\right) \\
&\times \prod_{j=0}^{J-1} dF_{\mathbf{C}_j(1,\overline{\mathbf{c}}_{j-1})|A,\overline{\mathbf{C}}_{j-1}(1),S_j(1,\overline{\mathbf{C}}_{j-1}(1))=1}\left(\mathbf{c}_j|A=1,S_j(1,\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(1)=\overline{\mathbf{c}}_{j-1}\right) \\
&= \int ... \int \mathbb{E}\left\{Y\ |A=1,S_J\ =1,\overline{\mathbf{c}}_{J-1}\right\}\prod_{j=2}^{J}\Pr\left(S_j=1|A=1,\overline{\mathbf{c}}_{j-1},S_{j-1}=1\right)\times\prod_{j=0}^{J-1} dF\ \ (\mathbf{c}_j|A=1,S_j=1,\overline{\mathbf{c}}_{j-1}) \\
&= \mathbb{E}\left\{Y\ S_J|A=1\right\}
\end{aligned}
$$

A similar argument shows that

$$\mathbb{E}\left\{S_J(1,\overline{\mathbf{C}}_{J-1}(1))\right\} = \mathbb{E}\left\{S_J|A=1\right\}$$

and therefore

$$\frac{\mathbb{E}\left\{Y(a=1)S_J(1,\overline{\mathbf{C}}_{J-1}(1))\right\}}{\mathbb{E}\left\{S_J(1,\overline{\mathbf{C}}_{J-1}(1))\right\}} = \mathbb{E}\left\{Y\ |S_J,A=1\right\}$$

Next, note that

$$\begin{aligned}\mu_{0,J} &= \mathbb{E}\left\{Y(a=0)|S_J(a,\overline{\mathbf{C}}_{J-1}(a^*))=1;\ a,a^*\in\{0,1\}\right\}\\ &= \frac{\mathbb{E}\left\{Y(a=0)S_J(0,\overline{\mathbf{C}}_{J-1}(0))S_J(1,\overline{\mathbf{C}}_{J-1}(0)\right\}}{\mathbb{E}\left\{S_J(0,\overline{\mathbf{C}}_{J-1}(0))S_J(1,\overline{\mathbf{C}}_{J-1}(0)\right\}}\end{aligned}$$

by the Concordant Survivorship Assumption. We then have that

$$\begin{aligned}
&\mathbb{E}\left\{Y(a=0)S_J(0,\overline{\mathbf{C}}_{J-1}(0))S_J(1,\overline{\mathbf{C}}_{J-1}(0)\right\}\\
&=\mathbb{E}\left[\mathbb{E}\left\{Y(a=0)S_J(0,\overline{\mathbf{C}}_{J-1}(0))S_J(1,\overline{\mathbf{C}}_{J-1}(0)|\overline{\mathbf{C}}_1\right\}\right]\\
&\vdots\\
&=\int\dots\int\mathbb{E}\left\{Y(a=0,\overline{\mathbf{c}}_{j-1})|S_J(1,\overline{\mathbf{c}}_{J-1})=S_J(0,\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_{J-1}(0)=\overline{\mathbf{c}}_{J-1}\right\}\\
&\times\prod_{j=2}^{J}\Pr\left(S_j(1,\overline{\mathbf{c}}_{j-1})=S_j(0,\overline{\mathbf{c}}_{j-1})=1\overline{\mathbf{C}}_{j-1}(0)=\overline{\mathbf{c}}_{j-1},S_{j-1}(1,\overline{\mathbf{c}}_{j-2})=S_{j-1}(0,\overline{\mathbf{c}}_{j-2})=1\right)\\
&\times\prod_{j=0}^{J-1}dF_{\mathbf{C}_j(0,\overline{\mathbf{c}}_{j-1})|\overline{\mathbf{C}}_{j-1}(0),S_j(1,\overline{\mathbf{C}}_{j-1}(0)),S_j(0,\overline{\mathbf{C}}_{j-1}(0))=1}\left(\mathbf{c}_j|S_j(1,\overline{\mathbf{c}}_{j-1})=S_j(0,\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(0)=\overline{\mathbf{c}}_{j-1}\right)\\
&=\int\dots\int\mathbb{E}\left\{Y(a=0,\overline{\mathbf{c}}_{j-1})|S_J(0,\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_{J-1}(0)=\overline{\mathbf{c}}_{J-1}\right\}\ \text{(NPSEM independence)}\\
&\times\prod_{j=2}^{J}\Pr\left(S_j(1,\overline{\mathbf{c}}_{j-1})=1|\overline{\mathbf{C}}_{j-1}(0)=\overline{\mathbf{c}}_{j-1},S_{j-1}(1,\overline{\mathbf{c}}_{j-2})=1\right)\ \text{(Sequential Monotonicity)}\\
&\times\prod_{j=0}^{J-1}dF_{\mathbf{C}_j(0,\overline{\mathbf{c}}_{j-1})|\overline{\mathbf{C}}_{j-1}(0),S_j(0,\overline{\mathbf{C}}_{j-1}(0))=1}\left(\mathbf{c}_j|S_j(0,\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(0)=\overline{\mathbf{c}}_{j-1}\right)\ \text{(NPSEM independence)}\\
&=\int\dots\int\mathbb{E}\left\{Y(a=0,\overline{c}_{j-1})|A=0,S_J(0,\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_{J-1}(0)=\overline{\mathbf{c}}_{J-1}\right\}\text{(NPSEM independence)}\\
&\times\prod_{j=2}^{J}\Pr\left(S_j(1,\overline{\mathbf{c}}_{j-1})=1|A=1,\overline{\mathbf{C}}_{j-1}(1)=\overline{\mathbf{c}}_{j-1},S_{j-1}(1,\overline{\mathbf{c}}_{j-2})=1\right)\ \text{(NPSEM independence)}\\
&\times\prod_{j=0}^{J-1}dF_{\mathbf{C}_j(0,\overline{\mathbf{c}}_{j-1})|A,\overline{\mathbf{C}}_{j-1}(0),S_j(0,\overline{\mathbf{C}}_{j-1}(0))=1}\left(\mathbf{c}_j|A=0,S_j(0,\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(0)=\overline{\mathbf{c}}_{j-1}\right)\ \text{(NPSEM independence)}\\
&=\int\dots\int\mathbb{E}\left(Y|A=0,S_J=1,\overline{\mathbf{C}}_{J-1}=\overline{\mathbf{c}}_{J-1}\right)\prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{c}}_{j-1}\right)\prod_{j=0}^{J-1}dG_{0,j}(\mathbf{c}_j;\overline{\mathbf{c}}_{j-1})
\end{aligned}$$

One can show using similar arguments that

$$\mathbb{E}\left\{S_J(0,\overline{\mathbf{C}}_{J-1}(0))S_J(1,\overline{\mathbf{C}}_{J-1}(0)\right\}$$
$$=\int\ldots\int\prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{c}}_{j-1}\right)\prod_{j=0}^{J-1}dG_{0,j}(\mathbf{c}_j;\overline{\mathbf{c}}_{j-1})$$

proving the result.

□

Proof of Theorem 3: $\widehat{\psi}_J$ converges in probability to the solution of the following population weighted normal equations:

$$\mathbb{E}\left\{S_J W_S W_A\left(1,A\right)^T\left(Y-\mu_{0,J}-\overline{\psi}_J A\right)\right\}=0$$

where $W_A=\left[p\left(\mathbf{C}_0\right)^A\left\{1-p\left(\mathbf{C}_0\right)\right\}^{1-A}\right]^{-1}$. It is straightforward to verify that under the assumptions of Theorem 3, the left hand-side of the equation in the above display is equal to:

$$\sum_{a=0}^{1}\mathbb{E}_a^*\left\{S_J\left(1,a\right)^T\left(Y-\mu_{0,J}-\overline{\psi}_J a\right)\right\}=0$$

where $\mathbb{E}_a^*$ is the expectation with respect to the law

$$\begin{cases} f\left(Y|A=0,S_J=1,\overline{\mathbf{C}}_{J-1}\right)\prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{C}}_{j-1}\right)\prod_{j=0}^{J-1}dG_{0,j}(\mathbf{C}_j;\overline{\mathbf{C}}_{j-1}) \text{ if } a=0 \\ f\left(Y,A=1,S_J=1\right) \text{ if } a=1 \end{cases}$$

giving the result.

□

Proof of Theorem 4: Let $\pi_1\left(a,\mathbf{C}_1\right)=\Pi\left(a\right)=\Pr(S=1|A=0,\mathbf{C}_1), B_a=\mathbb{E}\left(Y|A=a,S=1,\mathbf{C}_1\right),$

$G_a(\mathbf{C}_1) = F(\mathbf{C}_1|A = a)$. To prove the theorem, it suffice to show that $\mathbb{E}\left\{U(\mu_0, \pi_1^\dagger, B_1^\dagger)\right\} = 0$ if either $\pi_1^\dagger = \pi_1$, or $B_1^\dagger = B_1$ and $G_a^\dagger(\mathbf{c}_1) = G_a(\mathbf{c}_1)$, but not necessarily both hold, where

$$
\begin{aligned}
U(\mu_0, \pi_1^\dagger, B_1^\dagger) = (1-A)S\frac{\Pi^\dagger(1)}{\Pi^\dagger(0)}\left\{Y - B_0^\dagger\right\} \\
+ AB_0^\dagger\frac{dG_0^\dagger}{dG_1^\dagger}\left\{S - \Pi^\dagger(1)\right\} \\
+ \left\{(1-A)B_0^\dagger\Pi^\dagger(1) - \mu_0\right\},
\end{aligned}
$$

First assume that $\pi_1^\dagger = \pi_1$, then

$$
\begin{aligned}
&\mathbb{E}\left\{U(\mu_0, \pi_1, B_1^\dagger)\right\} \\
&= \mathbb{E}\left[(1-A)S\frac{\Pi(1)}{\Pi(0)}\left\{Y - B_0^\dagger\right\} + AB_0^\dagger\frac{dG_0^\dagger}{dG_1^\dagger}\left\{S - \Pi(1)\right\} + \left\{(1-A)B_0^\dagger\Pi(1) - \mu_0\right\}\right] \\
&= \mathbb{E}\left[(1-A)S\frac{\Pi(1)}{\Pi(0)}\left\{Y - B_0^\dagger\right\} + \left\{(1-A)B_0^\dagger\Pi(1) - \mu_0\right\}\right] \\
&= \mathbb{E}\left[(1-A)S\frac{\Pi(1)}{\Pi 0(0)}Y - \mu_0\right] \\
&= 0
\end{aligned}
$$

Next, suppose that $B_1^\dagger = B_1$ and $G_a^\dagger(\mathbf{c}_1) = G_a(\mathbf{c}_1)$, then

$$
\begin{aligned}
&\mathbb{E}\left\{U(\mu_0, \pi_1, B_1^\dagger)\right\} \\
&= \mathbb{E}\left[(1-A)S\frac{\Pi^\dagger(1)}{\Pi^\dagger(0)}\left\{Y - B_0\right\} + AB_0\frac{dG_0}{dG_1}\left\{S - \Pi^\dagger(1)\right\} + \left\{(1-A)B_0\Pi^\dagger(1) - \mu_0\right\}\right] \\
&= \mathbb{E}\left[AB_0\frac{dG_0}{dG_1}S - \mu_0\right] \\
&= 0
\end{aligned}
$$

proving the result.

□

Proof of Theorem 5: The proof is similar to that of Theorem 2; suppose that $\overline{a} \neq \overline{0}$, then

$$\begin{aligned}
\mu_J(\overline{a}) &= \mathbb{E}\left\{Y(\overline{a}) | S_J(\overline{a}, \overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{a})) = 1\right\} \text{ (Concordant Survivorship)} \\
&= \frac{\mathbb{E}\left\{Y(\overline{a})S_J(\overline{a}, \overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{a}))\right\}}{\mathbb{E}\left\{S_J(\overline{a}, \overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{a}))\right\}}
\end{aligned}$$

and, we have

$$\mathbb{E}\left\{Y(\overline{a})S_J(\overline{a},\overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0},\overline{\mathbf{C}}_{J-1}(\overline{a}))\right\}$$

$$=\mathbb{E}\left[\mathbb{E}\left\{Y(\overline{a})S_J(\overline{a},\overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0},\overline{\mathbf{C}}_{J-1}(\overline{a}))|\mathbf{C}_0\right\}\right]$$

$$\vdots$$

$$=\int\ldots\int\mathbb{E}\left\{Y(\overline{a},\overline{\mathbf{c}}_J)|S_J(\overline{a},\overline{\mathbf{c}}_{J-1})=S_J(\overline{0},\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_J\left(\overline{a}\right)=\overline{\mathbf{c}}_J\right\}$$

$$\times\prod_{j=2}^{J}\Pr\left(S_j(\overline{a}_{j-1},\overline{\mathbf{c}}_{j-1})=S_j(\overline{0}_{j-1},\overline{\mathbf{c}}_{j-1})=1|\overline{\mathbf{C}}_{j-1}\left(\overline{a}_{j-2}\right)=\overline{\mathbf{c}}_{j-1},S_{j-1}(\overline{a}_{j-2},\overline{\mathbf{c}}_{j-2})=S_{j-1}(\overline{0}_{j-1},\overline{\mathbf{c}}_{j-2})=1\right)$$

$$\times\prod_{j=0}^{J}dF_{\mathbf{C}_j(\overline{a}_{j-1},\overline{\mathbf{c}}_{j-1})|\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2}),S_j(\overline{a}_{j-1},\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2}))S_j(\overline{0}_{j-1},\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2}))=1}\left(\mathbf{c}_j|S_j(\overline{a}_{j-1},\overline{\mathbf{c}}_{j-1})\right.$$

$$\left.=S_j(\overline{0}_{j-1},\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2})=\overline{\mathbf{c}}_{j-1}\right)$$

$$=\int\ldots\int\mathbb{E}\left\{Y(\overline{a},\overline{\mathbf{c}}_J)|S_J(\overline{a},\overline{\mathbf{c}}_{J-1})=1,\overline{\mathbf{C}}_J\left(\overline{a}\right)=\overline{\mathbf{c}}_J\right\}\ \text{(NPSEM independence)}$$

$$\times\prod_{j=2}^{J}\Pr\left(S_j(\overline{0}_{j-1},\overline{\mathbf{c}}_{j-1})=1|\overline{\mathbf{C}}_{j-1}\left(\overline{a}_{j-2}\right)=\overline{\mathbf{c}}_{j-1},S_{j-1}(\overline{0}_{j-1},\overline{\mathbf{c}}_{j-2})=1\right)\ \text{(Sequential Monotonicity)}$$

$$\times\prod_{j=0}^{J}dF_{\mathbf{C}_j(\overline{a}_{j-1},\overline{\mathbf{c}}_{j-1})|\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2}),S_j(\overline{a}_{j-1},\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2}))=1}\left(\mathbf{c}_j|S_j(\overline{a}_{j-1},\overline{\mathbf{c}}_{j-1})=1,\overline{\mathbf{C}}_{j-1}(\overline{a}_{j-2})=\overline{\mathbf{c}}_{j-1}\right)$$

(NPSEM independence)

$$=\int\ldots\int\mathbb{E}\left\{Y|\overline{A}_J=\overline{a}_J,S_J=1,\overline{\mathbf{C}}_J=\overline{\mathbf{c}}_J\right\}\text{(NPSEM independence)}$$

$$\times\prod_{j=2}^{J}\Pr\left(S_j=1|\overline{A}_{j-1}=\overline{0}_{j-1},\overline{\mathbf{c}}_{j-1},S_{j-1}=1\right)\ \text{(NPSEM independence)}$$

$$\times\prod_{j=0}^{J}dF_{\mathbf{C}_j|\overline{C}_{j-1},\overline{A}_{j-1},S_j=1}\left(\mathbf{c}_j|\overline{A}_{j-1}=\overline{a}_{j-1},S_j=1,\overline{\mathbf{c}}_{j-1}\right)\ \text{(NPSEM independence)}$$

giving the result for

$$\mathbb{E}\left\{Y(\overline{a})S_J(\overline{a},\overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0},\overline{\mathbf{C}}_{J-1}(\overline{a}))\right\}$$

The expression for

$$\mathbb{E}\left\{S_J(\overline{a}, \overline{\mathbf{C}}_{J-1}(\overline{a}))S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{a}))\right\}$$

is similarly obtained. The result for $\mu_J\left(\overline{0}\right)$ is obtained by noting that

$$\begin{aligned}\mu_J\left(\overline{0}\right) &= \mathbb{E}\left\{Y(\overline{0})|S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))S_J(\overline{a}^*, \overline{\mathbf{C}}_{J-1}(\overline{0})) = 1 \text{ for all } \overline{a}^* \ \right\} \text{ (Concordant Survivorship)} \\ &= \frac{\mathbb{E}\left\{Y(\overline{0})S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))\ ) = 1\right\}}{\mathbb{E}\left\{\ S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))\ ) = 1\right\}} \text{ (Sequential Monotonicity)}\end{aligned}$$

and it is straightforward to verify that:

$$\begin{aligned}\mathbb{E}\left\{Y(\overline{0})S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))\ ) = 1\right\} = &\int ... \int \mathbb{E}\left\{Y|\overline{A}_J = \overline{0}, S_J = 1, \overline{\mathbf{C}}_J = \overline{\mathbf{c}}_J\right\} \\ &\times \prod_{j=2}^{J} \Pr\left(S_j = 1|\overline{A}_{j-1} = \overline{0}_{j-1}, \overline{\mathbf{c}}_{j-1}, S_{j-1} = 1\right) \\ &\times \prod_{j=0}^{J} dF_{\mathbf{C}_j|\overline{\mathbf{C}}_{j-1}, \overline{A}_{j-1}, S_j=1}\left(\mathbf{c}_j|\overline{A}_{j-1} = \overline{0}_{j-1}, S_j = 1, \overline{\mathbf{c}}_{j-1}\right)\end{aligned}$$

and the expression for $\mathbb{E}\left\{\ S_J(\overline{0}, \overline{\mathbf{C}}_{J-1}(\overline{0}))\ ) = 1\right\}$ is similarly derived.

□

Derivation of equation (17) :

$$
\begin{aligned}
&\mathbb{E}\left\{Y|A=0,\overline{\mathbf{C}}_{J-1}=\overline{\mathbf{c}}_{J-1},S_J=1\right\}\\
&=\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1\right\}\\
&\times\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)\\
&+\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1,S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=0\right\}\\
&\times\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=0|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)\\
&=\left[\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1,S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=0\right\}\right.\\
&\left.-\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1\right\}\right]\\
&\times\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=0|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)\\
&+\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1\right\}\\
&=\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1\right\}\\
&-t_J(\overline{\mathbf{c}}_{J-1})\times\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=0|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)
\end{aligned}
$$

Then, note that

$$\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)$$

$$=\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)$$

$$=\frac{\Pr\left(S_J(a=1,\overline{\mathbf{c}}_{J-1})S_J(a=0)=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_{J-1}(a=1,\overline{\mathbf{c}}_{J-2})S_{J-1}(a=0,\overline{\mathbf{c}}_{J-2})=1\right)}{\Pr\left(S_J(a=0)=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_{J-1}(a=0)=1\right)}$$

$$\times\Pr\left(S_{J-1}(a=1,\overline{\mathbf{C}}_{J-2}(a=0)=\overline{\mathbf{c}}_{J-2})=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_{J-1}(a=0)=1\right)$$

$$=\frac{\Pr\left(S_J(a=1,\overline{\mathbf{c}}_{J-1})=1|A=1,\overline{\mathbf{C}}_{J-1}(a=1)=\overline{\mathbf{c}}_{J-1},S_{J-1}(a=1,\overline{\mathbf{c}}_{J-2})=1\right)}{\Pr\left(S_J(a=0)=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_{J-1}(a=0)=1\right)}\ \text{(Sequential monotonicity and NPSEM independence)}$$

$$\times\Pr\left(S_{J-1}(a=1,\overline{\mathbf{C}}_{J-2}(a=0)=\overline{\mathbf{c}}_{J-2})=1|A=0,\overline{\mathbf{C}}_{J-2}(a=0)=\overline{\mathbf{c}}_{J-2},S_{J-1}(a=0)=1\right)\ \text{(NPSEM independence)}$$

thus by iterating, one obtains

$$\begin{aligned}
&\Pr\left(S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=1\right)\\
&=\prod_{j=2}^{J}\frac{\Pr\left(S_j(a=1,\overline{\mathbf{c}}_{j-1})=1|A=1,\overline{\mathbf{C}}_{j-1}(a=1)=\overline{\mathbf{c}}_{j-1},S_{j-1}(a=1,\overline{\mathbf{c}}_{j-2})=1\right)}{\Pr\left(S_j(a=0)=1|A=0,\overline{\mathbf{C}}_{j-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_{j-1}(a=0)=1\right)}\\
&=\frac{\prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{c}}_{j-1}\right)}{\prod_{j=2}^{J}\pi_j\left(0,\overline{\mathbf{c}}_{j-1}\right)}
\end{aligned}$$

which gives**:**

$$\begin{aligned}
&\mathbb{E}\left\{Y|A=0,\overline{\mathbf{C}}_{J-1}=\overline{\mathbf{c}}_{J-1},S_J=1\right\}\\
&=\mathbb{E}\left\{Y(a=0)|A=0,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1},S_J(a=0)=S_J(a=1,\overline{\mathbf{C}}_{J-1}(a=0)=\overline{\mathbf{c}}_{J-1})=1\right\}\\
&-t_J(\overline{\mathbf{c}}_{J-1})\times\left\{1-\frac{\prod_{j=2}^{J}\pi_j\left(1,\overline{\mathbf{c}}_{j-1}\right)}{\prod_{j=2}^{J}\pi_j\left(0,\overline{\mathbf{c}}_{j-1}\right)}\right\}
\end{aligned}$$

proving the result.Equation (16) is obtained by setting $J = 2$.

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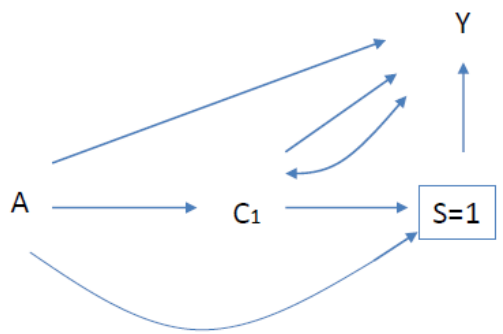

Figure. 1 Causal diagram associated with the NPSEM equations (1)-(4).

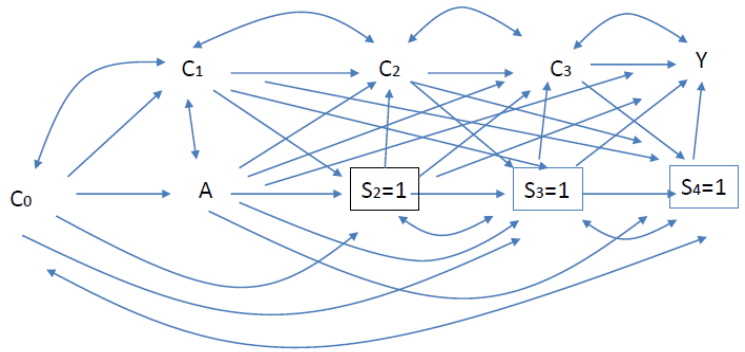

Figure. 2 Causal diagram associated with the NPSEM equations (11)-(14) at J=4.