Causal inference for semi-competing risks data

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SUMMARY

The causal effects of Apolipoprotein E $\epsilon4$ allele (APOE) on late-onset Alzheimer's disease (AD) and death are complicated to define because AD may occur under one intervention but not under the other, and because AD occurrence may affect age of death. In this article, this dual outcome scenario is studied using the semi-competing risks framework for time-to-event data. Two event times are of interest: a nonterminal event time (age at AD diagnosis), and a terminal event time (age at death). AD diagnosis time is observed only if it precedes death, which may occur before or after AD. We propose new estimands for capturing the causal effect of APOE on AD and death. Our proposal is based on a stratification of the population with respect to the order of the two events. We present a novel assumption utilizing the time-to-event nature of the data, which is more flexible than the often-invoked monotonicity assumption. We derive results on partial identifiability, suggest a sensitivity analysis approach, and give conditions under which full identification is possible. Finally, we present and implement nonparametric and semiparametric estimation methods under right-censored semi-competing risks data for studying the complex effect of APOE on AD and death.

Keywords: Alzheimer's disease; Bounds; Frailty model; Illness-death model; Principal stratification.

1. INTRODUCTION

Having at least one Apolipoprotein E $\epsilon4$ allele (APOE) has been associated with a substantial increase in risk of late-onset Alzheimer's disease (AD) (Alzheimer's Association, 2019). With the development of clustered regularly interspaced short palindromic repeats (CRISPR) for possible gene editing, researchers have begun contemplating gene editing on APOE as a preventive intervention against AD (Safieh *and others*, 2019). However, the standard average causal effect on AD is ill-defined because some study participants die without an AD diagnosis, and it is unknown whether APOE has a causal effect on survival (Corder *and others*, 1993; Dal Forno *and others*, 2002). When considering the impact of intervening on APOE, a holistic approach focusing on effects on both AD and death is desirable to help public health officials to weigh potential benefits and risks and to conclude whether gene editing of APOE is a viable intervention.

The semi-competing risks (SCR) framework have been used as a basis for studying AD and death jointly (Varadhan *and others*, 2014; Lee *and others*, 2017; Nevo *and others*, 2021a). More generally, SCR data arise when times to two events of interest are studied, nonterminal (e.g., disease diagnosis) and terminal

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(e.g., death) events. The nonterminal event is observed only if it precedes the terminal event, which may occur before or after the nonterminal event.

The illness-death model is often used for studying SCR data. It focuses on transition times between three different states: An initial state (state "0," healthy), a diseased state ("1," AD), and an absorbing state ("2," death). Possible transitions are $0 \rightarrow 1$, $0 \rightarrow 2$, and $1 \rightarrow 2$. Various time-to-event models have been suggested to analyze SCR data in this framework. Typically, inter-personal dependence between illness and death times is modeled via a random effect, known as frailty (Xu *and others*, 2010; Lee *and others*, 2017; Gorfine *and others*, 2021).

In the causal inference paradigm, the related "truncation by death" problem has been studied (Zhang and Rubin, 2003; Long and Hudgens, 2013; Tchetgen Tchetgen, 2014; Ding and Lu, 2017; Zehavi and Nevo, 2021). This problem arises when researchers aspire to compare outcomes between the treated and untreated groups at a fixed time point after the treatment was assigned, but some study participants may die prior to outcome collection, hence the average causal effect is not well-defined. Using principal stratification (Frangakis and Rubin, 2002), the survivor average causal effect (SACE) is the causal effect within the stratum of people who would have survived under both treatment values. A similar problem arises in vaccination studies, as vaccine effects on post-infection outcomes are well-defined only among those who would have been infected with or without vaccinating (Shepherd *and others*, 2007). The SACE is nonparametrically unidentifiable, unless strong assumptions are made. Therefore, researchers have developed bounds (Zhang and Rubin, 2003; Long and Hudgens, 2013) and sensitivity analyses (Shepherd *and others*, 2007). However, none of these papers apply to SCR data, where the time-to-event nature of both AD diagnosis and death must be addressed.

Robins (1995) utilized additional assumptions to show the average causal effect (not SACE) is identifiable when censoring time is always observed, and without distinguishing between censoring due to death or other reasons. More recently, two papers have considered causal questions for SCR data (Comment *and others*, 2019; Xu *and others*, 2020). These papers suggested Bayesian methods to estimate the time-varying SACE (TV-SACE) and restricted mean SACE (RM-SACE). These papers provide major improvement towards causal reasoning for SCR data. One of the works rely on parametric frailty-based illness-death models (Comment *and others*, 2019), while the other coupled a parametric sensitivity copula-based analysis with a nonparametric Bayesian method under an additional identifying assumption (Xu *and others*, 2020). Questions of nonparametric partial identifiability under weaker assumptions, or sensitivity analyses without the copula model, as well as frequentist estimation were all not addressed.

In this article, we define new causal estimands for capturing the causal effect of APOE on AD and death times within the SCR framework. The general idea resembles principal stratification in that we propose to stratify the population according to their potential outcomes. In Section 2, we propose new causal estimands for SCR data, that focus on effects defined within a fixed, not time-varying, population. As with principal stratification, membership status of this subpopulation is unobserved. In Section 3, we present novel causal assumptions under the SCR data structure that are motivated by the study of APOE and AD. Our new assumption termed *order preservation* is more flexible than the traditionally used monotonicity assumption (Zhang and Rubin, 2003). Section 3 also provides partial identifiability results for the proposed estimands under the new assumptions and full identifiability results under a bivariate frailty semiparametric illness-death model. In Section 4, we propose kernel-based nonparametric methods and a sensitivity analysis built upon a semiparametric illness-death frailty model. A fully reproducible simulation study is described in Section 5, before turning to the study of APOE effects on AD and death, in length, in Section 6. Concluding remarks are given in Section 7. The **R** package CausalSemiComp implements all the developed methodologies and is available from https://github.com/daniel258/CausalSemiComp and the reproducibility materials are available from https://github.com/daniel258/CausalSemiCompReproduce.

2. NOTATION AND CAUSAL ESTIMANDS

Let $T_1(a)$ and $T_2(a)$ be the times to AD diagnosis and death, respectively, had we set APOE level to $A = a$, with $A = 1$ indicating having at least one APOE $\epsilon 4$ allele, and $A = 0$ indicating no APOE $\epsilon 4$ alleles. Let $f_a(t_1, t_2)$ be the joint density function of $\{T_1(a), T_2(a)\}$ on $0 < t_1 \leq t_2$ for $a = 0, 1$. Because death may occur before AD diagnosis, $\Pr[T_1(a) < \infty] = \int_0^\infty \int_0^{t_2} f_a(t_1, t_2) \mathrm{d}t_1 \mathrm{d}t_2 < 1$. The event $T_1(a) = \infty$ or, stated differently, $T_1(a) > T_2(a)$ corresponds to not having AD under $A = a$. We defer assumptions on the joint distribution of $\{T_1(0), T_2(0)\}$ and $\{T_1(1), T_2(1)\}$ for later; these two pairs could never be observed simultaneously.

Consider the average causal effect of APOE on the survival time $E[T_2(1) - T_2(0)]$. Because APOE affects AD incidence (Alzheimer's Association, 2019), and because AD patients are likely to die earlier compared to the scenario they did not have AD (Tom *and others*, 2015), we would expect $E[T_2(1) - T_2(0)] < 0$, even if APOE does not carry an effect on age at death other than the effect resulting from earlier AD onset. Additionally, when focus is on AD, $E[T_1(1) - T_1(0)]$ is ill-defined, because $T_1(a) = \infty$ for some study units for either or both $a = 0$ and $a = 1$.

Therefore, causal inference for SCR data is entangled. Principal stratification effects suggested to address this challenge are defined within a strata of the population created by the potential values of a postrandomization variable, which is not the object of inquiry (Frangakis and Rubin, 2002). For SCR data, principal stratification approaches can be divided into two types: time-fixed and time-varying estimands. The time-fixed approach focuses on a single time point $\bar{t}$, say age 80, and defines the binary potential outcomes $\mathcal{S}(a) = I\{T_2(a) > \bar{t}\}$ and $\mathcal{Y}(a) = I\{T_1(a) \leq \bar{t}\}$ as the survival status and AD status at time $\bar{t}$ under APOE level $A = a$. The SACE $E[\mathcal{Y}(1) - \mathcal{Y}(0) | \mathcal{S}(1) = \mathcal{S}(0) = 1]$ compares the population-level risk of AD by age $\bar{t}$ with and without APOE only among those who would have survived until age $\bar{t}$ under both APOE statuses. Typically, strong assumptions are needed for identifying the SACE. One commonly made assumption is the *monotonicity* assumption $\mathcal{S}(1) \leq \mathcal{S}(0)$ (Zhang and Rubin, 2003; Ding and Lu, 2017; Zehavi and Nevo, 2021). That is, those surviving beyond time $\bar{t}$ and have APOE would also survive beyond $\bar{t}$ had they did not have APOE. A more recent approach (Comment *and others*, 2019; Xu *and others*, 2020) focuses on the TV-SACE causal effect $TV\text{-}SACE(t, r) = \Pr[T_1(1) < t | T_2(1) > r, T_2(0) > r] - \Pr[T_1(0) < t | T_2(1) > r, T_2(0) > r]$ for $t \leq r$. The $TV\text{-}SACE$ has two major advantages over the standard SACE: at each survival age r it compares nonterminal event rates in multiple time points, and it respects that the population of always-survivors depends on the chosen time r. Of note is that because the population changes with time, a change in $TV\text{-}SACE(t, r)$ as a function of r may reflect a change in the population or a change in the efficacy of the intervention.

2.1. *Population stratification and alternative estimands*

We propose alternative estimands, based on a single partition of the population. Unlike the partitions defining the SACE and TV-SACE, this single partition is not defined with respect to a specific (possibly varying) time point. Instead, we divide the population into four strata according to their AD and death "order." Because our partition involves the dual outcomes, we term it *population stratification*. Define the following four subpopulations with respect to the order of $T_1(a), T_2(a)$ for $a = 0, 1$. The "always-diseased" (*ad*) will be diagnosed with AD at some point of their life, regardless of their APOE status ($T_1(a) \leq T_2(a)$ for $a = 0, 1$); the "never-diseased" (*nd*) will die without having AD first, regardless of their APOE status ($T_1(a) > T_2(a)$ for $a = 0, 1$); the "harmed" (*dh*) would be diagnosed with AD prior to death only had they had APOE ($T_1(0) > T_2(0), T_1(1) \leq T_2(1)$); and the "protected" (*dp*) would be diagnosed with the disease only without APOE ($T_1(0) \leq T_2(0), T_1(1) > T_2(1)$). Let $\pi_{ad}, \pi_{nd}, \pi_{dh}$ and $\pi_{dp} = 1 - \pi_{ad} - \pi_{nd} - \pi_{dh}$ be the respective subpopulation proportions; see also Table 1.

Consider the stratum-specific causal estimands $\Pr[T_j(1) \leq t \mid g] - \Pr[T_j(0) \leq t \mid g]$ for $j = 1, 2$ and $g \in \{ad, nd, dh, dp\}$. Of note is that $\Pr[T_1(0) \leq t \mid dh] = \Pr[T_1(1) \leq t \mid dp] = 0$. Furthermore,

Table 1. *Population stratification for semi-competing risks data*

Name	Stratum definition	Stratum proportion
Always-diseased (ad)	$T_1(0) \leq T_2(0) \ \& \ T_1(1) \leq T_2(1)$	π_{ad}
Never-diseased (nd)	$T_1(0) > T_2(0) \ \& \ T_1(1) > T_2(1)$	π_{nd}
Disease-harmed (dh)	$T_1(0) > T_2(0) \ \& \ T_1(1) \leq T_2(1)$	π_{dh}
Disease-protected (dp)	$T_1(0) \leq T_2(0) \ \& \ T_1(1) > T_2(1)$	π_{dp}

the contrast $\Pr[T_2(1) \leq t \mid dh] - \Pr[T_2(0) \leq t \mid dh]$ is hard to interpret because under APOE, all *dh* would have AD before their death, but none of them would have AD before death under no APOE. A similar concern arise for the *dp* stratum. While $\pi_{dh} - \pi_{dp}$ is the additional proportion of AD patients in the population had the entire population had APOE versus had none of the population had APOE, this quantity should be interpreted with care. The *dh* stratum may include people for whom APOE induces early AD onset without affecting age of death and people for whom APOE prolongs survival long enough to be diagnosed with AD. Therefore, we henceforth focus on the following effects defined in the *ad* and *nd* strata

$$\Pr[T_2(1) \leq t \mid ad] - \Pr[T_2(0) \leq t \mid ad], \tag{2.1}$$

$$\Pr[T_2(1) \leq t \mid nd] - \Pr[T_2(0) \leq t \mid nd], \tag{2.2}$$

$$\Pr[T_1(1) \leq t \mid ad] - \Pr[T_1(0) \leq t \mid ad]. \tag{2.3}$$

Causal effects that better summarize the impact of A could be based on the restricted mean survival time (RMST). For a given time point $t^\star$, let $\mathcal{T}_j(a) = \min[T_j(a), t^\star], a, j = 0, 1$, and define

$$E[\mathcal{T}_2(1) - \mathcal{T}_2(0) \mid ad], \tag{2.4}$$

$$E[\mathcal{T}_1(1) - \mathcal{T}_1(0) \mid ad], \tag{2.5}$$

$$E\{[\mathcal{T}_2(1) - \mathcal{T}_1(1)] - [\mathcal{T}_2(0) - \mathcal{T}_1(0)] \mid ad\}, \tag{2.6}$$

$$E[\mathcal{T}_2(1) - \mathcal{T}_2(0) \mid nd]. \tag{2.7}$$

Each of the estimands characterizes a different causal effect of A on the outcomes within the *ad* or *nd* stratum. Effect (2.4) is the mean (possibly negative) gain in life expectancy caused by APOE, (2.5) is the effect of APOE on AD diagnosis age, and (2.6), which is obtained by subtracting (2.5) from (2.4), is the effect on the residual lifetime with AD. If, for example, the latter equals zero, it means the same life expectancy with AD is expected for those with and without APOE within the *ad* stratum. Effect (2.7) is also of great interest, as it is the effect of APOE on life expectancy among the *nd* population, thus it captures another form of APOE effect on survival. Other summary measures (e.g., median time-to-events) can also be used to define causal effects.

2.2. *Utility of proposed estimands and comparison to existing approaches*

Had we ignored follow-up after AD diagnosis, we would have a classical competing risks setup with the events AD diagnosis and AD-free death. Recently, there have been major advancements towards causal inference in the presence of competing events (Young *and others*, 2020; Stensrud *and others*, 2020; Nevo *and others*, 2021b). The *total effect* (Young *and others*, 2020) contrasts the proportion of AD patients by age t under APOE and no APOE for the entire population. A total effect can be also defined for the

APOE effect on survival. The total effects are useful to answer a multitude of research questions, but one should be aware that interpretation can be complicated. For example, it may seems as if APOE protects against AD-free death, simply because it induces earlier onset of AD. The *direct effect* (Young *and others*, 2020) of APOE on AD contrasts the counterfactual AD risk with and without APOE had we eliminated the competing event for the entire population. To our knowledge, such intervention is not available for either AD or death. Stensrud *and others* (2020) proposed alternative casual estimands for competing-risks data, based on conceptual separation of the treatment into components such that each component affects a different competing event. The SCR framework has been increasingly used for aging research; see Varadhan *and others* (2014) for review and comparisons with competing risks. Unlike competing risks, the SCR viewpoint additionally considers follow-up after the occurrence of the nonterminal event. Therefore, the SCR framework presents an opportunity to study the dual outcomes of interest holistically, while considering simultaneously benefits and risks with respect to both events. As we demonstrate below, the proposed estimands can be used, for example, for studying the effect of APOE on AD age-of-onset among those who would have AD regardless of APOE status, or the effect of APOE on survival, separately for those would and would not have AD regardless of APOE status. The latter effect cannot be studied if follow-up after AD is ignored. In addition, SCR data provide partial information about the dependence of the two event times (conditionally on $T_1 \leq T_2$), which is unidentifiable from competing-risks data, a fact often leveraged in models for SCR data.

A second approach views AD diagnosis as a time-varying and possibly death-truncated mediator of the effect of APOE on survival. Interventional direct and indirect effects are more appealing for such a task, as the assumption of no common causes of AD and death affected by APOE seems too strong; see Lin *and others* (2017). The mediation approach is desirable when the question of interest is the extent to which AD mediates the effect of APOE on survival. In this work, we make no direct attempt to answer such questions. Our approach does not specify the role of AD as a mediator. For example, APOE may affect cognitive decline underpinning AD, and this cognitive decline may affect death not only through earlier AD onset. Therefore, it is possible that AD is a proxy of an unmeasured mediator in addition to its possible, though not necessary, own mediating role.

Nevertheless, a connection of the proposed estimands to the mediation literature can be made. Let $M(a) = I\{T_1(a) < T_2(a)\}$. One may argue that estimands (2.4) and (2.7) resemble principal stratum direct effects (PSDEs) under $M(0) = M(1) = 1$ and $M(0) = M(1) = 0$, respectively. As highlighted by VanderWeele (2011), PSDEs are generally interpretable as direct effects. In our motivating example, one may consider (2.4) as the effect of APOE on survival which is not mediated by the occurrence of AD.

From a public health policy point of view, the decision whether CRISPR should be used to eliminate APOE must consider the population effect on the dual outcomes of AD and death. Our proposed estimands offer a number of information pieces needed when considering the population health and economic value of such intervention. In Section 6, we estimate *ad* proportion to be 35% and the median gain in AD-free years by age 100 (analog of estimand (2.5)) to be 2.01 years (95% CI 1.92–2.09). This means that eliminating APOE would delay in at least 2 years AD diagnosis for at least half of those who would have AD under any APOE status. To complement this quantity, (2.4) is the gain in survival in the same population; the median gain is estimated to be 3.00 years (95% CI 2.93–3.07), meaning that eliminating APOE extends life for at least half of those within the *ad* strata by at least 3 years. The APOE intervention effect is not limited to the *ad* strata. In Section 6, we estimate the *nd* proportion to be 53%, and the median gain in survival by age 100 to be 1.99 years (95% CI 1.90–2.08). Considered collectively, the results provide initial evidence for desirable effects of eliminating APOE on both AD and survival in the population. A careful inspection will help regulators and public health officials to weigh the consequences of APOE intervention at scale. The TV-SACE and RM-SACE do not provide the above-described information, but they can complement it by providing insight into heterogeneity of the effect across time.

3. Identifiability

The focus of this section is on assumptions and identifiability. Methods for estimation and inference under right censoring are developed in Section 4. Let (A, T_1, T_2) be the actual APOE and event times. Throughout this article, we assume no interference between individuals and the following two standard assumptions.

Assumption 1 *Consistency.* $T_1 = T_1(1)A + T_1(0)(1 - A)$ and $T_2 = T_2(1)A + T_2(0)(1 - A)$.

Assumption 2 *Weak Ignorability,* $A \perp\!\!\!\perp \{T_1(a), T_2(a)\}$ for $a = 0, 1$.

In many observational studies that lack randomization, a conditional version of Assumption 2, conditionally on covariates, is more plausible; see also Section 3.4.

3.1. *Bounds*

Because principal stratum effects are not identified from the data unless additional assumptions are leveraged, researchers often develop bounds (Zhang and Rubin, 2003; Long and Hudgens, 2013). Here, we present various bounds for the causal effects based on the identifiable distribution of (A, T_1, T_2), constructed differently depending on the assumptions a researcher is willing to make. First, we present a new assumption, tailored for SCR data.

Assumption 3 *Order preservation.* If $T_1(0) \leq T_2(0)$, then $T_1(1) \leq T_2(1)$.

Under Assumption 3, anyone who would have been diagnosed with AD without having APOE, would also have AD had they had APOE, but not necessarily at the same age. It is consistent with the overwhelming evidence that APOE significantly increases the risk of AD (Alzheimer's Association, 2019). Assumption 3 is more flexible than the often-invoked monotonicity assumption, in that it acknowledges the realistic scenario that A may impact survival time for either direction. Specifically, it allows that $T_2(0) - T_2(1)$ and $T_1(0) - T_1(1)$ are of different signs at the unit level. To see this, observe that $T_1(1) \leq T_2(1)$ implies $T_2(0) - T_2(1) \leq [T_2(0) - T_1(0)] + [T_1(0) - T_1(1)]$. Figure 1 presents potential AD and death times for seven hypothetical units, differing at the timing and order of the potential event times. The figure depicts examples of units existing under both assumptions, and units that their existence violates one of the assumptions (or both). Of note is that for a unit with no AD under either APOE status, Assumption 3 holds, while monotonicity would not hold if APOE prolongs the lifetime of that unit. Finally, Assumption 3 implies that the *dp* stratum is empty, that is, $\pi_{dp} = 0$.

As is typically the case in truncation-by-death problems, even under Assumptions 1–3, none of the causal effects (2.1)–(2.7) are nonparametrically identifiable. These effects are however partially identifiable, in the sense that the data, coupled with the assumptions, provide bounds on these effects. For any event $\mathcal{Q}$, let $F_{j|\mathcal{Q}}(t) = \Pr(T_j \leq t | \mathcal{Q})$, $S_{j|\mathcal{Q}}(t) = 1 - F_{j|\mathcal{Q}}(t)$ and $\eta_{\mathcal{Q}} = \Pr(T_1 \leq T_2 | \mathcal{Q})$. Under Assumptions 1–3, $\Pr(T_2(0) \leq t \mid ad), \Pr(T_2(1) \leq t \mid nd)$ and $\Pr(T_1(0) \leq t \mid ad)$ are identified, while $\Pr(T_2(1) \leq t \mid ad), \Pr(T_2(0) \leq t \mid nd)$ and $\Pr(T_1(1) \leq t \mid ad)$ are only partially identified. The following proposition establishes partial identifiability under Assumptions 1–3.

Proposition 1 Under Assumptions 1–3, effects (2.1)–(2.3) are partially identified by

$$\mathcal{L}_{2,ad}(t) \leq \Pr[T_2(1) \leq t | ad] - \Pr[T_2(0) \leq t | ad] \leq \mathcal{U}_{2,ad}(t), \tag{3.8}$$

$$\mathcal{L}_{2,nd}(t) \leq \Pr[T_2(1) \leq t | nd] - \Pr[T_2(0) \leq t | nd] \leq \mathcal{U}_{2,nd}(t), \tag{3.9}$$

$$\mathcal{L}_{1,ad}(t) \leq \Pr[T_1(1) \leq t | ad] - \Pr[T_1(0) \leq t | ad] \leq \mathcal{U}_{1,ad}(t), \tag{3.10}$$
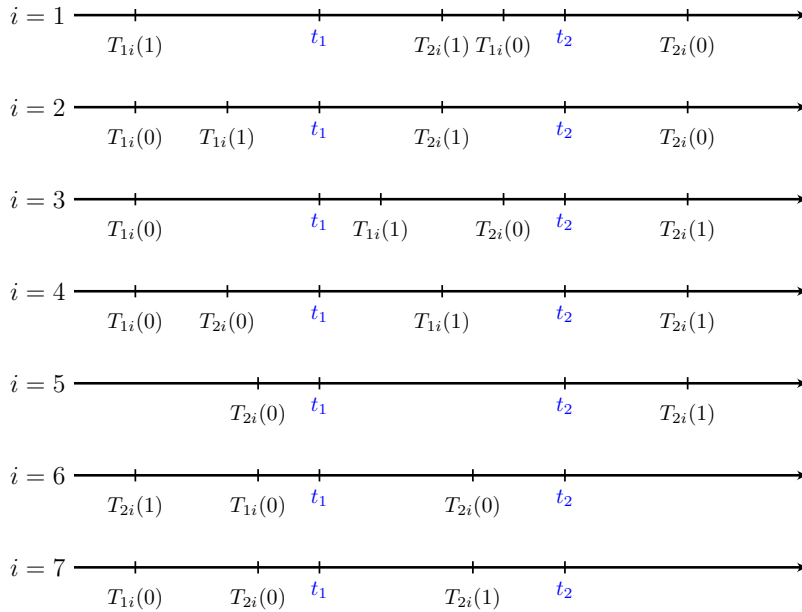
Fig. 1. Illustration of Assumption 3 and its distinction compared to the monotonicity assumption using seven hypothetical units. Units 1 and 2 are allowed under both assumptions, Assumption 3 and monotonicity. For unit 1, APOE expedites both AD and death, but in a way that AD remains before death. For unit 2, APOE impedes AD but expedites death. Nevertheless, unit 2 would live long enough under APOE for AD to occur. Similar protective effect occurs for unit 3, however, this unit violates monotonicity at time t_2 (as an example). Unit 4 also violates monotonicity (at t_1 and t_2) but not Assumption 3. Unit 5 does not suffer from AD under any APOE value, hence it is allowed by Assumption 3 but it does violate monotonicity (at t_1 and t_2) as AD carries a protective effect against death. Unit 6 violates Assumption 3 but not monotonicity. Arguably, for this unit the APOE effect on death is so strong the unit would have died under APOE before getting the chance to have AD. Finally, unit 7 violates both assumptions.

where

$$\mathcal{L}_{2,ad}(t) = \max\left\{0, 1 - \frac{S_{2|A=1}(t)}{\eta_{A=0}}\right\} - F_{2|A=0,T_1 \leq T_2}(t),$$

$$\mathcal{U}_{2,ad}(t) = \min\left\{1, F_{2|A=1}(t)\frac{\eta_{A=1,T_2 \leq t}}{\eta_{A=0}}\right\} - F_{2|A=0,T_1 \leq T_2}(t),$$

$$\mathcal{L}_{2,nd}(t) = F_{2|A=1,T_1 > T_2}(t) - \min\left\{1, F_{2|A=0}(t)\frac{1-\eta_{A=0,T_2 \leq t}}{1-\eta_{A=1}}\right\},$$

$$\mathcal{U}_{2,nd}(t) = F_{2|A=1,T_1 > T_2}(t) - \max\left\{0, 1 - \frac{S_{2|A=0}(t)}{1-\eta_{A=1}}\right\},$$

$$\mathcal{L}_{1,ad}(t) = \max\left\{0, 1 - \frac{S_{1|A=1}(t)}{\eta_{A=0}}\right\} - F_{1|A=0,T_1 \leq T_2}(t),$$

$$\mathcal{U}_{1,ad}(t) = \min\left\{1, \frac{F_{1|A=1}(t)}{\eta_{A=0}}\right\} - F_{1|A=0,T_1 \leq T_2}(t).$$

(3.11)

The proof is given in Section A.1 of the Supplementary material available at *Biostatistics* online. Under Assumptions 1–3, the strata proportions are identified by $\pi_{ad} = \eta_{A=0}$, $\pi_{dh} = \eta_{A=1} - \eta_{A=0}$, $\pi_{nd} = 1 - \eta_{A=1}$. RMST effects (2.5)–(2.7) are (partially) identified by recalling that for any nonnegative random variable

T and any fixed time $t^* > 0$, we have $E(\min\{T, t^*\}) = \int_0^{t^*} [1 - \Pr(T \leq t)]dt$. Had we had unlimited uncensored data, we could have calculated the bounds using $F_{2|A=a}(t), F_{2|A=a,T_1 \leq T_2}(t), \eta_{A=a}$ and $\eta_{A=a,T_2 \leq t}$. As for $F_{1|A=a}(t)$, we could have used $F_{1|A=a}(t) = \eta_{A=a} F_{1|A=a,T_1 \leq T_2}(t)$.

Generally, bounds derived under additional assumptions might be narrower (Zhang and Rubin, 2003; Long and Hudgens, 2013). Of course, these assumptions need to be plausible in the scientific problem at hand for the bounds to be valid. One particular bound that may not be informative enough is $\mathcal{L}_{1,ad}(t)$. As t increases, the second term $F_{1|A=0,T_1 \leq T_2}(t)$ get closer to one while the first term is not, because $\Pr(T_1 < \infty | A = 1) < 1$. As a remedy for this problem, consider the following assumption and proposition providing a more informative lower bound for (2.3).

Assumption 4 For a given t, $\Pr[T_1(1) \leq t | ad] \geq \Pr[T_1(1) \leq t | dh]$.

This assumption resembles the ranked average score assumption (Zhang and Rubin, 2003), but tailored for time-to-event data. Assumption 4 reflects researcher belief that the *ad* are generally more frail (with respect to AD), and hence are expected to be diagnosed at earlier ages than those in the *dh* stratum. For example, if those in the *ad* stratum are more likely than those at the *dh* stratum to have other AD risk factors. In practice, Assumption 4 can hold for some, all, or none of the values of t.

PROPOSITION 2 Under Assumptions 1–3, for any t for which Assumption 4 holds, $\Pr[T_1(1) \leq t | ad] - \Pr[T_1(0) \leq t | ad]$ is partially identified by $\widetilde{\mathcal{L}}_{1,ad}(t) \leq \Pr[T_1(1) \leq t | ad] - \Pr[T_1(0) \leq t | ad] \leq \mathcal{U}_{1,ad}(t)$, where $\widetilde{\mathcal{L}}_{1,ad}(t) = F_{1|A=1,T_1 \leq T_2}(t) - F_{1|A=0,T_1 \leq T_2}(t)$ and $\mathcal{U}_{1,ad}(t)$ is given in Proposition 1.

The proof is given in Section A.2 of the Supplementary material available at *Biostatistics* online. In some studies, the obtained bounds, with or without additional assumptions, might be too wide to have practical utility. Therefore, following Long and Hudgens (2013), we develop narrower bounds utilizing a preintervention discrete covariate Z. In our study, Z can be, for example, gender. An adjusted version of Proposition 1 can be obtained under the following assumption.

Assumption 5 $A \perp\!\!\!\perp \{Z, T_1(a), T_2(a)\}$ for $a = 0, 1$.

For example, we show in Section A.3 of the Supplementary material available at *Biostatistics* online that under Assumptions 1, 3, and 5, adjusted bounds for (2.1) are given by $\mathcal{L}_{2,ad}^Z(t), \mathcal{U}_{2,ad}^Z(t)$, where

$$
\mathcal{L}_{2,ad}^Z(t) = \sum_z \nu(z) \left[\max\left\{ 0, 1 - \frac{S_{2|A=1,Z=z}(t)}{\eta_{A=0,Z=z}} \right\} - F_{2|A=0,T_1 \leq T_2,Z=z}(t) \right],
$$

$$
\mathcal{U}_{2,ad}^Z(t) = \sum_z \nu(z) \left[\min\left\{ 1, F_{2|A=1,Z=z}(t) \frac{\eta_{A=1,T_2 \leq t,Z=z}}{\eta_{A=0,Z=z}} \right\} - F_{2|A=0,T_1 \leq T_2,Z=z}(t) \right],
$$

(3.12)

and $\nu(z) = \Pr(Z = z | A = 0, T_1 \leq T_2)$. Similarly, adjusted bounds $\mathcal{L}_{2,nd}^Z(t), \mathcal{U}_{2,nd}^Z(t)$ and $\mathcal{L}_{1,ad}^Z(t), \mathcal{U}_{1,ad}^Z(t)$ can be constructed. Furthermore, the following proposition establishes that the adjusted bounds are always within the unadjusted bounds.

PROPOSITION 3 Under Assumptions 1, 3 and 5, $\mathcal{L}_{2,ad}(t) \leq \mathcal{L}_{2,ad}^Z(t)$ and $\mathcal{U}_{2,ad}(t) \geq \mathcal{U}_{2,ad}^Z(t)$.
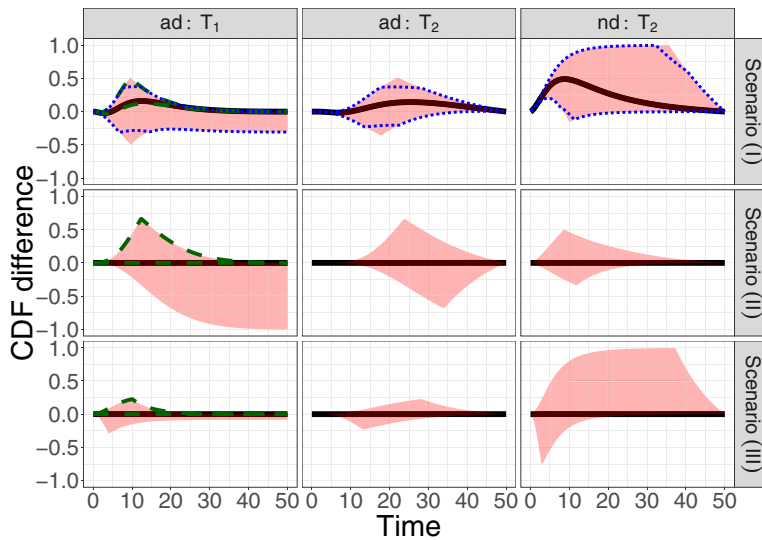
Fig. 2. True causal effects (2.1)–(2.3) and different bounds under three simulated scenarios. The bounds derived in Proposition 1, $\{\mathcal{L}_{1,ad}(t), \mathcal{U}_{1,ad}(t)\}$, $\{\mathcal{L}_{2,ad}(t), \mathcal{U}_{2,ad}(t)\}$, and $\{\mathcal{L}_{2,nd}(t), \mathcal{U}_{2,nd}(t)\}$, are in pink shade. The blue dotted lines are the adjusted bounds $\{\mathcal{L}_{1,ad}^{Z}(t), \mathcal{U}_{1,ad}^{Z}(t)\}$, $\{\mathcal{L}_{2,ad}^{Z}(t), \mathcal{U}_{2,ad}^{Z}(t)\}$, and $\{\mathcal{L}_{2,nd}^{Z}(t), \mathcal{U}_{2,nd}^{Z}(t)\}$. The green dashed lines are the bounds $\{\widetilde{\mathcal{L}}_{1,ad}(t), \widetilde{\mathcal{U}}_{1,ad}(t)\}$.

The proof is given in Section A.4 of the Supplementary material available at *Biostatistics* online. Proposition 3 is the analog of Proposition 1 in Long and Hudgens (2013), who developed bounds for binary outcomes. Of note is that due to finite-sample variation, Proposition 3 may not hold empirically. Therefore, as suggested by Long and Hudgens (2013), the bounds $\max\{\mathcal{L}_{2,ad}(t), \mathcal{L}_{2,ad}^{Z}(t)\}$ and $\min\{\mathcal{U}_{2,ad}(t), \mathcal{U}_{2,ad}^{Z}(t)\}$ can be used.

Figure 2 illustrates the various bounds under three different scenarios. The data-generating mechanism (DGM) and the resulting per-stratum cumulative distribution functions are described in Section D.1 of the Supplementary material available at *Biostatistics* online. Under Scenario (I) (top row), Assumptions 3 and 4 hold, and $A = 1$ shorten the *ad* time-to-disease and time-to-death, and *nd* die faster under $A = 1$. The bounds $\{\mathcal{L}_{1,ad}(t), \mathcal{U}_{1,ad}(t)\}$, $\{\mathcal{L}_{2,ad}(t), \mathcal{U}_{2,ad}(t)\}$, and $\{\mathcal{L}_{2,nd}(t), \mathcal{U}_{2,nd}(t)\}$ (in pink shade) are quite wide in this scenario. The bound $\widetilde{\mathcal{L}}_{1,ad}(t)$ (dashed green line) is far more informative, being only slightly lower than the true difference (black solid curve). The adjusted bounds (blue dotted lines) were narrower than the unadjusted bounds, most notably for t values for which the unadjusted bounds are very wide. For the causal effect on time-to-disease within the *ad* (top left corner) the narrower bound is obtained as $\{\widetilde{\mathcal{L}}_{1,ad}(t), \mathcal{U}_{1,ad}^{Z}(t)\}$. The bounds for time-to-death among the *nd* are quite wide. This is likely because there is least information on this group from the observed data, as the true stratum probabilities were $(\pi_{ad}, \pi_{nd}, \pi_{dh}) = (0.49, 0.15, 0.36)$.

For further illustration of the latter point, consider the two bottom rows of Figure 2, both under null effects. In Scenario (II), the *nd* stratum comprised most of the population, $(\pi_{ad}, \pi_{nd}, \pi_{dh}) = (0.13, 0.59, 0.28)$, and the bounds were quite narrow for the within *nd* effect (2.2), and less informative for the *ad*. In Scenario (III), π_{ad} was substantial, $(\pi_{ad}, \pi_{nd}, \pi_{dh}) = (0.70, 0.07, 0.23)$, and the bounds were quite narrow only for causal effects within the *ad*. In conclusion, if one of the proportions π_{ad} or π_{nd} is large enough, the bounds can be useful, and a covariate Z may help to create narrower bounds. Under Assumption 4, the lower bound $\widetilde{\mathcal{L}}_{1,ad}(t)$ is quite informative.

3.2. *Identification by frailty assumptions*

We turn to present stronger assumptions under which effects (2.1)–(2.3) are identified from the data. The proposed overarching strategy formulates two illness-death models and tying them together via a bivariate frailty random variable $\boldsymbol{\gamma} = (\gamma_0, \gamma_1)$. For $a = 0, 1$, let

$$\lambda_{01}(t|a, \boldsymbol{\gamma}) = \lim_{\Delta \to 0} \Delta^{-1} \Pr[T_1 \in [t, t + \Delta)|A = a, T_1 \geq t, T_2 \geq t, \boldsymbol{\gamma}], \quad t > 0,$$

$$\lambda_{02}(t|a, \boldsymbol{\gamma}) = \lim_{\Delta \to 0} \Delta^{-1} \Pr[T_2 \in [t, t + \Delta)|A = a, T_1 \geq t, T_2 \geq t, \boldsymbol{\gamma}], \quad t > 0,$$

$$\lambda_{12}(t|a, t_1, \boldsymbol{\gamma}) = \lim_{\Delta \to 0} \Delta^{-1} \Pr[T_2 \in [t, t + \Delta)|A = a, T_1 = t_1, T_2 \geq t, \boldsymbol{\gamma}], \quad t > t_1 > 0$$

be the three cause-specific hazard functions under the SCR setting (Xu *and others*, 2010), associated with the transitions $j \to k, jk = 01, 02, 12$ (0: healthy, 1: AD, 2: death); see Figure C.1 of the Supplementary material available at *Biostatistics* online for illustration. The strategy of how to model the distribution of $\boldsymbol{\gamma}$ dictates two forms of dependence, cross-world and within-world. A frailty-based approach with parametric assumptions on the hazard functions, coupled with Bayesian estimation was considered by Comment *and others* (2019). The authors assumed $\gamma_0 = \gamma_1$ leading to identifiability of the causal effects. That $\gamma_0 = \gamma_1$ implies the same dependence between AD and death times in both worlds. However, it would generally not hold unless all effect modifiers can be measured and correctly accounted for. We extend this approach by incorporating a sensitivity parameter ρ that encapsulates the cross-world, and unidentifiable, dependence.

Assumption 6 There exists a bivariate random variable $\boldsymbol{\gamma} = (\gamma_0, \gamma_1)$ such that

(i) $A \perp\!\!\!\perp \{T_1(a), T_2(a), \gamma_a\}$ for $a = 0, 1$.
(ii) Given $\boldsymbol{\gamma}$, the joint distribution of the potential event times can be factored as follows

$$f[T_1(0), T_2(0), T_1(1), T_2(1)|\boldsymbol{\gamma}] = f[T_1(0), T_2(0)|\gamma_0]f[T_1(1), T_2(1)|\gamma_1], \qquad (3.13)$$

where $f(\cdot)$ denotes a density function of a possibly multivariate random variable.
(iii) The frailty variable operates multiplicatively on the hazard function $\lambda_{jk}(t|a, \boldsymbol{\gamma}) = \gamma_a \widetilde{\lambda}_{jk}(t|a)$ for $jk = 01, 02$ and $\lambda_{12}(t|a, t_1, \boldsymbol{\gamma}) = \gamma_a \widetilde{\lambda}_{12}(t|a, t_1)$ for $a = 0, 1$, for some $\widetilde{\lambda}_{jk}$ functions.
(iv) The probability density function of $\boldsymbol{\gamma}, f_{\boldsymbol{\theta}}(\boldsymbol{\gamma})$, is known up to a finite dimensional parameter $\boldsymbol{\theta}$ that is identifiable from the observed data distribution.

Part (i) of Assumption 6 adapts Assumption 2 for the frailty. Part (ii) implies a cross-world independence conditionally on the unobserved $\boldsymbol{\gamma}$. That is, the inclusion of the frailty represents a model for the collection of unobserved covariates governing the cross-world dependence. This model induces marginal (with respect to $\boldsymbol{\gamma}$) complex dependence and conditional independence between $\{T_1(0), T_2(0)\}$ and $\{T_1(1), T_2(1)\}$. Parts (iii) and (iv) guarantee identification of the observed data distribution. As with any parametric model, one cannot expect the model to hold exactly. Nevertheless, it is well-known that usually misspecification of the frailty distribution leads to only small bias in the estimated cumulative incidence function (of the observed data distribution), integrated over the frailty distribution; see Gorfine *and others* (2021) and references therein.

While other specifications are possible, we assume that (γ_0, γ_1) are correlated Gamma variables, with mean one, variances θ_0 and θ_1, and correlation ρ. The frailty variances θ_0 and θ_1 are identifiable from the data, while ρ is unidentifiable and is supplied by the researcher. Taking $\rho = 1$ is analogous to the

approach of Comment *and others* (2019), and results in point identification. The following proposition provides identification as a function of ρ, thus allowing a more flexible consideration of the unidentifiable cross-world dependence.

PROPOSITION 4 Under Assumptions 1 and 6, the causal effects (2.1)–(2.3) are identified by

$$
\Pr[T_2(1) \leq t|ad] - \Pr[T_2(0) \leq t|ad]
$$
$$
= \int_0^\infty \int_0^\infty [F_{2|T_1 \leq T_2, A=1, \gamma_1}(t) - F_{2|T_1 \leq T_2, A=0, \gamma_0}(t)}] \frac{\eta_{A=0,\gamma_0} \eta_{A=1,\gamma_1} f_{\boldsymbol{\theta}}(\boldsymbol{\gamma}) \mathrm{d}\boldsymbol{\gamma}}{\int_0^\infty \int_0^\infty \eta_{A=0,\gamma_0'} \eta_{A=1,\gamma_1'} f_{\boldsymbol{\theta}}(\boldsymbol{\gamma}') \mathrm{d}\boldsymbol{\gamma}'},
$$

$$
\Pr[T_2(1) \leq t|nd] - \Pr[T_2(0) \leq t|nd]
$$
$$
= \int_0^\infty \int_0^\infty [F_{2|T_1 > T_2, A=1, \gamma_1}(t) - F_{2|T_1 > T_2, A=0, \gamma_0}(t)] \frac{(1 - \eta_{A=0,\gamma_0})(1 - \eta_{A=1,\gamma_1}) f_{\boldsymbol{\theta}}(\boldsymbol{\gamma}) \mathrm{d}\boldsymbol{\gamma}}{\int_0^\infty \int_0^\infty (1 - \eta_{A=0,\gamma_0'})(1 - \eta_{A=1,\gamma_1'}) f_{\boldsymbol{\theta}}(\boldsymbol{\gamma}') \mathrm{d}\boldsymbol{\gamma}'},
$$

$$
\Pr[T_1(1) \leq t|ad] - \Pr[T_1(0) \leq t|ad]
$$
$$
= \int_0^\infty \int_0^\infty [F_{1|T_1 \leq T_2, A=1, \gamma_1}(t) - F_{1|T_1 \leq T_2, A=0, \gamma_0}(t)] \frac{\eta_{A=0,\gamma_0} \eta_{A=1,\gamma_1} f_{\boldsymbol{\theta}}(\boldsymbol{\gamma}) \mathrm{d}\boldsymbol{\gamma}}{\int_0^\infty \int_0^\infty \eta_{A=0,\gamma_0'} \eta_{A=1,\gamma_1'} f_{\boldsymbol{\theta}}(\boldsymbol{\gamma}') \mathrm{d}\boldsymbol{\gamma}'},
$$

where for any event $\mathcal{Q}$, $F_{j|\mathcal{Q},\boldsymbol{\gamma}}(t) = \Pr(T_j \leq t|\mathcal{Q}, \boldsymbol{\gamma})$, $j = 1, 2$.

The proof is given in Section A.5 of the Supplementary material available at *Biostatistics* online. RMST-like estimands (2.4)–(2.7) are identified by suitable integration over t. Figure 3 illustrates the RMST effects (2.4), (2.5), and (2.7) under the DGM described in Section 4 and Section D.1 of the Supplementary material available at *Biostatistics* online, with equal variances $\theta = \theta_0 = \theta_1$ and as a function of ρ. Stratum proportions varied between 41–45% for *ad* stratum and 8–12% for the *nd* stratum. The causal RMST effects, calculated at $t^\star = 15$, were sensitive to ρ when the stratum proportion was very small and the frailty variance was large and were otherwise quite robust to ρ.

3.3. *Right censoring*

Time-to-event outcome data are often not fully observed for all individuals due to right censoring. Two issues arise when considering right censoring. The first is identification of the causal estimand, considered in this section, and the second is how to estimate the different quantities and provide inference, which is embedded in the nonparametric and semiparametric methods presented in Section 4. Let $C(a)$ be the right-censoring time under $A = a$. Assumption 2 is adjusted for the case of censoring by assuming $A \perp\!\!\!\perp \{T_1(a), T_2(a), C(a)\}$ for $a = 0, 1$. We also assume within-world independent censoring, namely that $\{T_1(a), T_2(a)\} \perp\!\!\!\perp C(a)$ for $a = 0, 1$. In our study, this assumption asserts that, under each APOE value, the two event times and censoring time are independent. We also assume that $\Pr(T_j(a) > \bar{c}) > 0$ for $j = 1, 2$ with $\bar{c}$ being the end of follow-up time. Combining the weak ignorability and within-world independent-censoring assumptions together, and by Assumption 1, we get the standard independent censoring assumption for SCR data $T_1, T_2 \perp\!\!\!\perp C$, with C being the censoring time under A.

3.4. *Covariates inclusion*

Often the ignorability and independent censoring assumptions are more plausible when made conditionally on covariates X. Assumption 6 is also more plausible when made conditionally on covariates. For simplicity, we use the same vector X for all assumptions to hold. In Section A.6 of the Supplementary
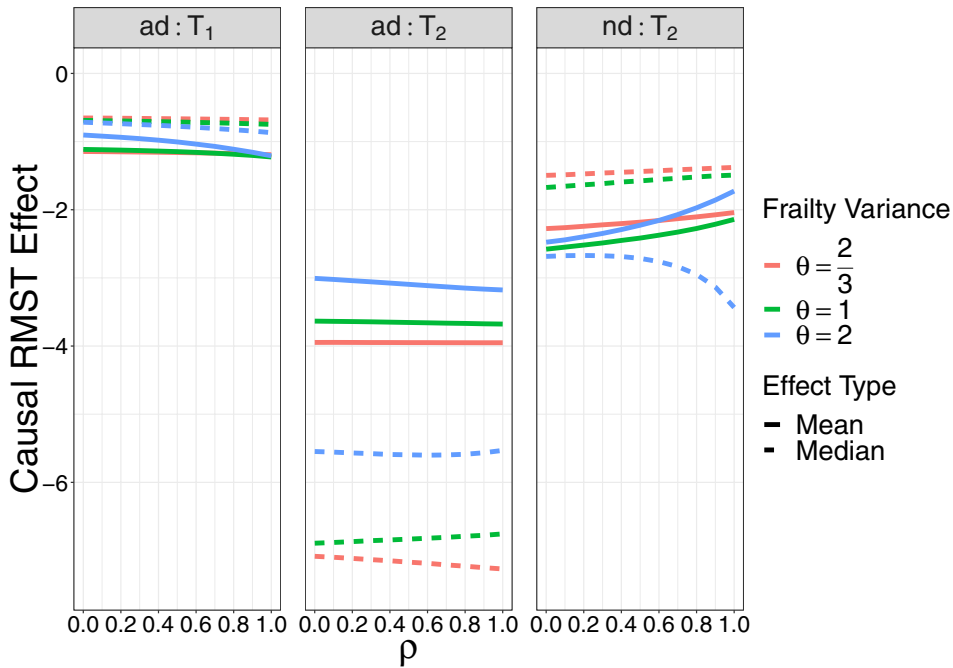
Fig. 3. Causal restricted mean and median survival time effects at $t^\star = 15$ as a function of the frailty variance $\theta = \theta_0 = \theta_1 = 2/3, 1, 2$, (corresponding to Kendall's $\tau = 1/4, 1/3, 1/2$) as a function of the correlation between the frailty variables $\rho \in [0, 1]$.

material available at *Biostatistics* online, we adapt Propositions 1 and 4 to include covariates. An additional reason to include covariates is to improve estimators' efficiency. In our study (Section 6), we use gender and race as covariates. Note that the role of X is different from the role of the covariate Z we utilized in Section 3.1.

While a variety of statistical models have been used for SCR data, how to elucidate information on causal effects is typically overlooked and, in practice, focus is often on specific regression coefficients. Therefore, our work enables translation of existing model results into knowledge on causal effects. With this is mind, we focus on frequentist estimation of causal effects (2.4)–(2.7) under semiparametric frailty models that align with Assumption 6.

4. ESTIMATION AND INFERENCE

We now turn to estimation and inference from right-censored SCR data. We first propose nonparametric estimators, before considering semiparametric models. For the nonparametric estimators, the quantities of interest are the building blocks of the bounds, namely $\eta_{A=a}, \eta_{A=a,T_2 \leq t}, S_{1|A=a}, S_{2|A=a}, S_{1|A=a,T_1 \leq T_2}, S_{2|A=a,T_1 \leq T_2},$ and $S_{2|A=a,T_1 > T_2}$ (for $a = 0, 1$). For the semiparametric estimation, we focus on a frailty-based proportional-hazard model that allows estimation of causal effects utilizing Proposition 4.

For each participant $i = 1, ..., n$ denote by Z_i a covariate that is used for obtaining sharper bounds (when available), by X_i a vector of baseline covariates (when available), by $A_i \in \{0, 1\}$, the APOE value, and by T_{ij} the AD $(j = 1)$ and death $(j = 2)$ times. Let also C_i be the censoring time. The data for each unit are $(Z_i, X_i, A_i, \widetilde{T}_{i1}, \delta_{i1}, \widetilde{T}_{i2}, \delta_{i2})$ where $\widetilde{T}_{i1} = \min(T_{i1}, T_{i2}, C_i)$ and $\widetilde{T}_{i2} = \min(T_{i2}, C_i)$ are the observed times,

and $\delta_{i1} = I\{\widetilde{T}_{i1} = T_{i1}\}$ and $\delta_{i2} = I\{\widetilde{T}_{i2} = T_{i2}\}$ are the indicators of AD and death, respectively. Finally, $Y_{ij}(t) = I\{t \le \widetilde{T}_{ij}\}$ are the at-risk processes.

4.1. *Nonparametric estimation*

We suggest to estimate $S_{2|A=a}(t)$ by the Kaplan–Meier (KM) estimator. Regarding $S_{1|A=a}(t)$,

$$S_{1|A=a}(t) = \Pr(T_1 > t|A = a) = -\int_0^\infty S_{1|A=a,T_2=s}[\min(t,s)]\mathrm{d}S_{2|A=a}(s), \tag{4.14}$$

because for $t > s$, $S_{1|A=a,T_2=s}(t) = S_{1|A=a,T_2=s}(s)$, that is, among those who die at time s, no new disease cases are possible later than s. The function $S_{1|A=a,T_2=s}$ is well-defined, and thus can be estimated nonparametrically.

We propose to estimate $S_{1|A=a,T_2=s}(t)$ by a kernel-smoothed KM estimator (Beran, 1981) within the $\{A = a, \delta_2 = 1\}$ group. Let $K(\cdot)$ be a kernel function ($K(t) \ge 0$, $\int K(t)\mathrm{d}t = 1$), and let $h_n \to 0$ be a sequence of bandwidths. In practice, one might consider a separate bandwidth for each level of A. For simplicity of presentation, we assume h_n is the same for both $a = 0, 1$. Let $Q(s,a;h_n) = \sum_{i=1}^n I\{A_i = a\}\delta_{i2}K[(s - T_{i2})/h_n]$, and $W_i(s,a;h_n) = I\{A_i = a\}\delta_{i2}K[(s - T_{i2})/h_n]/Q(s,a;h_n)$. The kernel-smoothed KM estimator for $S_{1|A=a,T_2=s}(t)$ is then defined by

$$\widehat{S}_{1|A=a,T_2=s}(t) = \prod_{i=1}^n \left[1 - \frac{W_i(s,a;h_n)}{\sum_{j=1}^n Y_{1j}(\widetilde{T}_{i1})W_j(s,a;h_n)} \right]^{\delta_{i1}\delta_{i2}I\{A_i=a,\widetilde{T}_{i1}\le t\}}. \tag{4.15}$$

We propose to estimate $\eta_{A=a}$ in similar fashion utilizing that

$$\eta_{A=a} = \Pr(T_1 \le T_2|A = a) = -\int_0^\infty F_{1|A=a,T_2=t}(t)\mathrm{d}S_{2|A=a}(t). \tag{4.16}$$

In Section C.1 of the Supplementary material available at *Biostatistics* online, we give similar explicit formulas for $\eta_{A=a,T_2\le t}, S_{1|A=a,T_1\le T_2}(t), S_{2|A=a,T_1\le T_2}(t)$, and $S_{2|A=a,T_1>T_2}(t)$. Covariate-adjusted bounds (3.12) are estimated at each level of Z and averaged by $\widehat{v}(z) = \widehat{\Pr}(Z = z)\widehat{\eta}_{Z=z}/\widehat{\Pr}(T_1 \le T_2)$. A sketch of the proof for the asymptotic properties of the proposed estimators using existing results for the KM estimator and kernel-smoothed KM estimator is provided in Section C.2 of the Supplementary material available at *Biostatistics* online; see also Akritas and Van Keilegom (2003).

4.2. *Semiparametric frailty models*

Under Assumption 6, we propose to use the following proportional hazard specification

$$\begin{aligned}
\lambda_{01}(t|a, \boldsymbol{X}, \gamma) &= \gamma_a\lambda_{01}^0(t|a)\exp(\boldsymbol{X}^T\boldsymbol{\beta}_{01}^a) \quad, t > 0 \\
\lambda_{02}(t|a, \boldsymbol{X}, \gamma) &= \gamma_a\lambda_{02}^0(t|a)\exp(\boldsymbol{X}^T\boldsymbol{\beta}_{02}^a) \quad, t > 0 \\
\lambda_{12}(t|t_1, a, \boldsymbol{X}, \gamma) &= \gamma_a\lambda_{12}^0(t|a)\exp(\boldsymbol{X}^T\boldsymbol{\beta}_{12}^a) \quad, t > t_1 > 0,
\end{aligned} \tag{4.17}$$

where $\lambda_{jk}^0(t|a), jk = 01, 02, 12, a = 0, 1$ are unspecified baseline hazard functions. Define also the cumulative baseline hazard functions, $\Lambda_{jk}^0(t|a) = \int_0^t \lambda_{jk}^0(u|a)\mathrm{d}u$, and let $\boldsymbol{\beta} = (\boldsymbol{\beta}_{01}^{0T}, \boldsymbol{\beta}_{02}^{0T}, \boldsymbol{\beta}_{12}^{0T}, \boldsymbol{\beta}_{01}^{1T}, \boldsymbol{\beta}_{02}^{1T}, \boldsymbol{\beta}_{12}^{1T})^T$, and $\boldsymbol{\Lambda}_0 = (\Lambda_{01}^0(\cdot|a), \Lambda_{02}^0(\cdot|a), \Lambda_{12}^0(\cdot|a))$ for $a = 0, 1$. Finally, let $\boldsymbol{\psi} = (\boldsymbol{\Lambda}_0, \boldsymbol{\beta}, \boldsymbol{\theta})$ be the collection of

parameters to be estimated from the data. For prospectively collected data with all participants being AD-free at study starting time, the likelihood function is proportional to

$$\mathcal{L}(\boldsymbol{\psi}) = \prod_{i=1}^{n} \left\{ [\lambda_{01}^{0}(\widetilde{T}_{i1}|A_i)]^{\delta_{i1}} [\lambda_{02}^{0}(\widetilde{T}_{i1}|A_i)]^{(1-\delta_{i1})\delta_{i2}} [\lambda_{12}^{0}(\widetilde{T}_{i2}|A_i)]^{\delta_{i1}\delta_{i2}} \right. \tag{4.18}$$

$$\left. \exp\left[\delta_{i1} \boldsymbol{X}_i^T \boldsymbol{\beta}_{01}^{A_i} + (1-\delta_{i1})\delta_{i2} \boldsymbol{X}_i^T \boldsymbol{\beta}_{02}^{A_i} + \delta_{i1}\delta_{i2} \boldsymbol{X}_i^T \boldsymbol{\beta}_{12}^{A_i} \right] (-1)^{\delta_{i1}+\delta_{i2}} \phi_{A_i}^{(\delta_{i1}+\delta_{i2})}(s_i) \right\},$$

where $\phi_a^{(0)}(s) = E\{\exp\{-s\gamma_a\}\}$, $\phi_a^{(q)}$ is the qth derivative of $\phi_a^{(0)}(s)$ with respect to s, $q = 1, 2$, and $s_i = \sum_{j=1}^{2} \exp(\boldsymbol{X}_i^T \boldsymbol{\beta}_{0j}^{A_i}) \Lambda_{0j}^{0}(\widetilde{T}_{i1}|A_i) + \delta_{i1} \exp(\boldsymbol{X}_i^T \boldsymbol{\beta}_{12}^{A_i}) [\Lambda_{12}^{0}(\widetilde{T}_{i2}|A_i) - \Lambda_{12}^{0}(\widetilde{T}_{i1}|A_i)]$. The likelihood derivation follows from SM3 of Gorfine *and others* (2021). In Section C.3 of the Supplementary material available at *Biostatistics* online, we present an EM algorithm for maximizing (4.18). The estimation phase ignores the unidentifiable component ρ. Assumptions on the joint distribution of (γ_0, γ_1) are used to map the estimator $\hat{\boldsymbol{\psi}}$ into estimates of causal effects. Upon estimating $\hat{\boldsymbol{\psi}}$, the quantities in the identifying formulas from Proposition 4 can be calculated by numerical integration or Monte Carlo simulations, as we do in Section 5.

5. SIMULATIONS

To assess the finite-sample properties of the proposed estimators, we conducted simulations under various scenarios with 1,000 simulation iterations per scenario. Sample size was $n = 2000$ and different censoring rates were considered. The DGM initially followed (4.17) with Weibull baseline hazards, two covariates, and Gamma frailty as described in Section 3.2 with $\theta_0 = \theta_1$ for simplicity. Treatment was randomized with $\Pr(A = 1) = 0.5$ and observed event times (pre censoring) were created by Assumption 1. Details on the different DGMs, analyses and comprehensive results are presented in Section D of the Supplementary material available at *Biostatistics* online and described briefly here.

For the nonparametric estimation, we considered the scenarios previously used in Figure 2. Assumption 3 was imposed by re-simulating those initially at the *dh* stratum. For the smoothed KM estimator, default choices of the **R** package prodlim were used (Gerds, 2019). Standard errors were estimated by bootstrap (sampling at the unit level) with 100 repetitions. For all parameters considered, bias was negligible, standard errors were well estimated and 95% Wald-type confidence intervals had satisfactory empirical coverage rate.

For the semiparametric estimation, data was generated under model (4.17) and was not restricted to follow Assumption 3. Gamma frailties were simulated with $\rho = 0, 0.5, 1$ and equal variances $\theta = 2/3, 1, 2$, corresponding to Kendall's $\tau = 1/4, 1/3, 1/2$ between $T_1(a)$ and $T_2(a)$. For each simulated dataset, we fitted two illness-death frailty models for $A = 0, 1$ using the EM algorithm (Section C.3 of the Supplementary material available at *Biostatistics* online). Frailty variances were estimated separately and then combined (Section D.2.2 of the Supplementary material available at *Biostatistics* online). RMST causal effects were estimated by a Monte Carlo integration using the estimated baseline hazards $\widehat{\boldsymbol{\Lambda}}$, coefficients $\widehat{\boldsymbol{\beta}}$ and $\widehat{\theta}$ (Section D.2 of the Supplementary material available at *Biostatistics* online). Standard errors were estimated using bootstrap with 100 repetitions. Generally, the empirical bias of the estimated mean and median RMST effects was relatively negligible, standard errors were well estimated, and coverage provabilities were satisfactory. The regression coefficients, baseline hazard functions, and frailty variance were all also well estimated (Section D.3 of the Supplementary material available at *Biostatistics* online).

6. DATA ANALYSIS

The Adult Changes in Thought (ACT) Study is a prospective cohort study focused on dementia in the elderly. Starting from 1994, AD-free participants of age 65 and older from the Seattle metropolitan area
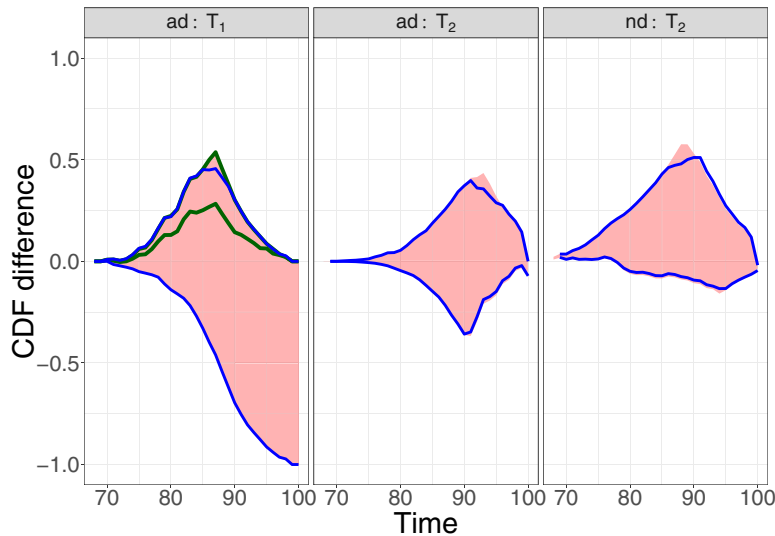
Fig. 4. Bounds for principal effects of APOE on AD and death based on the ACT data. In pink shade the simple bounds, in blue bounds adjusted for gender, and in green bounds based on Assumption 4.

have been recruited (Kukull *and others*, 2002). Our analyses include the binary variables gender and race (white/nonwhite). Other available covariates (e.g., years of education) were not used as they are determined post-intervention. Out of 4453 participants, 1783 (40%) were censored prior to any event, 211 (5%) were diagnosed with AD and then censored, 1635 (37%) died without an AD diagnosis, and 824 (19%) were diagnosed with AD and died during follow-up. APOE was present for 1073 (24%) study participants. Because APOE is inherited and independent of other inherited traits, the ignorability assumptions seem plausible in this study.

Figure 4 presents the estimated bounds for causal effects (2.1)–(2.3) under Assumption 3 (pink shade), utilizing gender as an additional covariate (blue), and under the additional Assumption 4 (green, for (2.3) only). Assumptions 3 and 4 seem reasonably plausible in this application, because APOE is a well-known strong predictor of AD. The *ad* proportion π_{ad} was estimated to be 35% (95% CI 32%–37%). The bounds $[\widetilde{\mathcal{L}}_{1,ad}(t), \mathcal{U}^Z_{1,ad}(t)]$ (bottom green and top blue) demonstrate that APOE induces earlier AD onset within the *ad* stratum. The bounds do not allow for definite conclusions regarding the effect of APOE on death, and the inclusion of the variable gender had only minor effect. Focusing on the *nd* stratum, its proportion was estimated to be 53% (95% CI 49%–58%), meaning the two stratum of interest together comprise the vast majority of the population. Whether APOE had a positive or negative effect on survival in the *nd* is unclear, although the lower bound was larger than zero for early ages. The *dh* stratum proportion was estimated to be 12% (95% CI 7%–17%), meaning that had the entire population had APOE, we would have expect a 12% increase of in the proportion of people with AD diagnosis sometime in their lifetime, compared to the scenario that none of the population had APOE.

In the semiparametric analysis under Assumption 6, two illness-death models (4.17) were fitted using the EM algorithm, and included gender and race as covariates X (SM Table E.15 presents the estimated coefficients). Because participants in the ACT were recruited in varying ages, data were left truncated. We followed the approximation of Nielsen *and others* (1992), by replacing all risk indicators $I\{t \leq \widetilde{T}_{ij}\}$ with $I\{R_i \leq t \leq \widetilde{T}_{ij}\}$, where R_i is the age at recruitment. The estimated frailty variance was $\hat{\theta} = 0.042$ (SE: 0.005), corresponding to Kendall's τ of 0.02. Turning to causal effects (Table 2), significant long-term negative effects of APOE on AD onset within the *ad* stratum were estimated; those with APOE

Table 2. *Estimated RMST causal effects of APOE on AD and death times within the ad and nd strata.*
Effects presented are mean (ATE) and median (MTE) differences. Results presented for $\rho = 0.5$. The
empirical distribution of gender and race in the data was used for calculating RMST effects

Stratum	$t^\star$	AD		Death	
		$\widehat{ATE}$ (95% CI)	$\widehat{MTE}$ (95% CI)	$\widehat{ATE}$ (95% CI)	$\widehat{MTE}$ (95% CI)
ad	15	−0.04 (−0.12 to 0.04)	0.00 (−0.07 to 0.07)	−0.61 (−0.7 to −0.52)	−1.00 (−1.09 to −0.91)
	25	−1.28 (−1.35 to −1.20)	−2.00 (−2.07 to −1.92)	−2.52 (−2.61 to −2.43)	−3.00 (−3.08 to −2.92)
	35	−1.82 (−1.89 to −1.74)	−2.01 (−2.09 to −1.92)	−2.42 (−2.5 to −2.35)	−3.00 (−3.07 to −2.93)
nd	15			−0.13 (−0.22 to −0.05)	0.00 (−0.08 to 0.08)
	25			−0.56 (−0.65 to −0.48)	−1.00 (−1.08 to −0.92)
	35			−1.75 (−1.84 to −1.67)	−1.99 (−2.08 to −1.90)

are expected to receive an AD diagnosis approximately 2 years earlier. Additionally, death at earlier age was expected in both strata under APOE. For $t^\star = 15$ (age 80), effects were zero for the *nd* stratum and negative though small for the *ad*. For $t^\star = 25, 35$ (ages 90,100), effects were negative in both strata, but stronger for the *ad*. The estimated effects did not change substantially as a function of ρ.

To summarize the findings, APOE was found to expedite AD development within the *ad* stratum. APOE was shown to have harmful effect on long-term age at death in both strata only under Assumption 6 and the semiparametric modeling.

7. Discussion

It has been increasingly acknowledged that considering dual outcomes may provide unique information about the scientific problem in hand, especially in the presence of death as a competing event. While the SCR framework allows for consideration of dual outcomes, questions of causality under this framework were only recently began to be studied. To study causal effects of APOE on AD and death, we proposed new estimands built upon a population stratification approach.

Population stratification may suffer from similar disadvantages to principal stratification - that one cannot know the stratum a unit belongs to at baseline, and that the *ad* and *nd* strata may be small or irregular subsets of the population. When the *ad* and/or the *nd* strata comprise small part of the population, the TV-SACE and TV-RMST can be more informative. The TV-SACE and RM- SACE are also attractive when heterogeneity in treatment effect across time is of interest. When the goal is to assess the extent to which an intervention effect is mediated through a disease, a mediation approach should be preferred. Finally, when interest lies in the disease event only, causal estimands from the competing events literature might be more appealing.

We presented two overarching strategies towards studying the proposed causal estimands. The large-sample bounds we developed are built upon a set of assumptions a researcher is willing to make explicitly on the relation between potential outcomes under two different interventions. The frailty-based approach models cross-world dependence via semiparametric assumptions and carries out a sensitivity analysis as a function of the sensitivity parameter. One disadvantage of the latter is that the exact restrictions imposed on the potential outcomes beyond the conditional independence are implicit. Our sensitivity analysis strategy resembles the approach of Xu *and others* (2020) in that a correlation parameter for the cross-world dependence is introduced together with a distribution assumption. We used a frailty approach, while Xu *and others* (2020) assumed a Gaussian copula model for the joint distribution function of $(T_1(a), T_2(a))$ conditionally on X. Xu *and others* (2020) then considered a flexible Bayesian regression model.

8. Software

Our **R** package `CausalSemiComp` (Version 1.0.0) implements the proposed methodology and is available from https://github.com/daniel258/CausalSemiComp.

Supplementary material

Supplementary material is available at http://biostatistics.oxfordjournals.org.

Acknowledgments

The authors thank two anonymous reviewers and the Associate Editor for helpful comments that improved the article.

Conflict of Interest: None declared.

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