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Targeted learning in real-world comparative effectiveness research with time-varying interventions

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In comparative effectiveness research (CER), often the aim is to contrast survival outcomes between exposure groups defined by time-varying interventions. With observational data, standard regression analyses (e.g., Cox modeling) cannot account for time-dependent confounders on causal pathways between exposures and outcome nor for time-dependent selection bias that may arise from informative right censoring. Inverse probability weighting (IPW) estimation to fit marginal structural models (MSMs) has commonly been applied to properly adjust for these expected sources of bias in real-world observational studies. We describe the application and performance of an alternate estimation approach in such a study. The approach is based on the recently proposed targeted learning methodology and consists in targeted minimum loss-based estimation (TMLE) with super learning (SL) within a nonparametric MSM. The evaluation is based on the analysis of electronic health record data with both IPW estimation and TMLE to contrast cumulative risks under four more or less aggressive strategies for treatment intensification in adults with type 2 diabetes already on 2+ oral agents or basal insulin. Results from randomized experiments provide a surrogate gold standard to validate confounding and selection bias adjustment. Bootstrapping is used to validate analytic estimation of standard errors. This application does the following: (1) establishes the feasibility of TMLE in real-world CER based on large healthcare databases; (2) provides evidence of proper confounding and selection bias adjustment with TMLE and SL; and (3) motivates their application for improving estimation efficiency. Claims are reinforced with a simulation study that also illustrates the double-robustness property of TMLE. Copyright © 2014 John Wiley & Sons, Ltd.

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1. Introduction

In comparative effectiveness research (CER), a frequent aim is to contrast survival outcomes between exposure groups defined by time-varying interventions. In observational CER studies, these effects are represented by marginal structural models (MSMs), and their investigation is complicated by the time-dependent confounding and informative right censoring that are expected with longitudinal data. Standard regression techniques (e.g., Cox regression) are inadequate [1, 2] to account not only for time-dependent confounders on causal pathways between the exposures and outcome but also for time-dependent selection bias that may arise from right censoring [3]. To date, inverse probability weighting (IPW) estimation has been the solution of choice to fit MSM in real-world CER studies [4–9] despite the early development of an alternate estimation approach, augmented-IPW (A-IPW) estimation [10–14], which is both doubly robust and locally efficient. These two properties may translate in practice into the following: (1) more reliable effect estimates because double robustness provides two chances for proper confounding and selection bias adjustment (i.e., inference can remain valid even if the treatment and action mechanisms on which IPW estimation relies are not estimated consistently) and (2) more precise effect estimates compared with IPW estimates and hence the possibility for earlier detection of differ-

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ential safety or effectiveness signals. The complexity of the implementation of A-IPW estimation with time-varying exposures largely explains its limited use in practice [14, 15].

Recently, targeted learning [16] was proposed as an alternative to IPW and A-IPW estimation for drawing causal inferences in problems with both point treatment and time-varying interventions of interest. Targeted learning encompasses a general doubly robust and efficient estimation methodology that is coupled with super learning (SL) [17] to data-adaptively estimate the nuisance parameters on which relies estimation of the estimand of interest. While this approach and its asymptotic properties were derived from a formal theoretical framework and mostly tested with simulated and real-word point treatment data, there remains a need for further practical evaluation of this general methodology for applications in problems with time-varying interventions. Early evaluation of targeted learning for CER with time-varying exposures based on real-world data from a large healthcare database [18] revealed the practical complexity of a targeted maximum likelihood estimation algorithm initially proposed for implementation of targeted Learning with time-varying interventions. Subsequently, an alternate algorithm that greatly simplifies applications of targeted learning in problems with time-varying interventions and a limited number of time-varying covariates was developed [19]. Current experience with these algorithms precludes however their routine applications in real-world CER problems that often require controlling for medium-dimensional to high-dimensional time-varying covariates. More recently, van der Laan and Gruber [20] derived a targeted minimum loss-based estimation (TMLE) algorithm for evaluating the effect of time-varying interventions based on a general targeted learning estimation road map [21, 22] applied with a key identifiability result from Bang and Robins [14]. Compared with previously proposed targeted learning algorithms, TMLE further simplifies implementation of targeted learning in CER studies with time-varying interventions and in particular if control for medium-dimensional to high-dimensional time-varying covariates is needed.

Using both a real-world CER study and a simulation study, we first aim to describe the application of this algorithm, evaluate its computation burden and assess its performance with confounding and selection bias adjustment. Motivation for preferring a TMLE approach over an IPW estimation approach in CER includes the following: (i) the mitigation of concerns over violation of the assumption of consistent estimation of the treatment and right-censoring mechanisms (double-robustness property) and (ii) a possible gain in the precision of the effect estimates with non-rare outcomes (efficiency property). Our second objective here is to evaluate the potential for gain in estimation efficiency with TMLE over IPW estimation in practice.

Our evaluation is first based on the analysis of electronic health record data with both IPW estimation and TMLE to contrast cumulative risks under four more or less aggressive strategies for treatment intensification (TI) in adults with type 2 diabetes on 2+ oral agents or basal insulin. Results from previous randomized experiments provide a surrogate gold standard to validate confounding and selection bias adjustment. Bootstrapping is used to validate analytic estimation of standard errors (SEs) on which is based the evaluation of potential efficiency gains with TMLE and SL. Second, analyses of simulated data are presented to support claims we make based on the previous real data analysis and also to demonstrate the double-robustness property of TMLE.

2. Evaluation with a real-world comparative effectiveness research study

In this section, we describe the CER question, answers from previous randomized studies and the observational study on which is based the evaluation in this report. We also introduce formal notation for representing the data structure and the parameter of interest in this analysis.

2.1. Research question and previous trial results

It has long been hypothesized that aggressive glycemic control is an effective strategy to reduce the occurrence of common and devastating microvascular and macrovascular complications of type 2 diabetes (T2DM). A major goal of clinical care of T2DM is minimization of such complications through a variety of pharmacological treatments and interventions to achieve recommended levels of glucose control. The progressive nature of T2DM results in frequent revisiting of treatment decisions for many patients as glycemic control deteriorates. Widely accepted stepwise guidelines start treatment with metformin and then add a secretagogue if control is not reached or deteriorates. Insulin or (less frequently) a third oral agent is the next step. Thus, it is common for T2DM patients to be on multiple glucose-lowering medications.

Current recommendations specify a target hemoglobin A1c of <7% for most patients [23, 24]. However, evidence supporting the effectiveness of a blanket recommendation is inconsistent across several outcomes [25–31], especially when intensive antidiabetic therapy is required. In this report, we aim to evaluate the impact of progressively more aggressive glucose-lowering strategies on the development or progression of albuminuria, a microvascular complication in T2DM.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) clinical trials published from 2008 to 2010 [32, 33], intensive glucose-lowering strategies using multiple classes of glucose-lowering agents succeeded in reducing A1c levels substantially. In the ADVANCE trial, the more intensive therapy arm aimed to reach an A1c level <6.5% and achieved a mean A1c level of 6.5%, compared with a mean level of 7.3% in the control arm. In the ACCORD trial, the more intensive arm aimed for an A1c of <6% and achieved a mean A1c of 6.4% (vs. 7.5% in controls). There are substantial data from both trials [35, 36] to support the hypothesis [37, 38] that, in general, those with T2DM who are treated to lower A1c levels may have lower rates of onset and progression of albuminuria (e.g., hazard ratio: 0.79, 0.66–0.93 in ADVANCE).

2.2. An observational, multicenter, retrospective, cohort study

The effects of intensive treatment remain uncertain, and the optimal target levels of A1c for balancing benefits and risks of therapy are not clearly defined. In addition, no additional major trials addressing these questions are underway.

For these reasons, by using the electronic health records from patients of seven sites of the Health Maintenance Organization Research Network [39], a large retrospective cohort study of adults with T2DM was assembled to evaluate the impact of progressively more aggressive glucose-lowering strategies on several clinical outcomes. To properly account for time-dependent confounding and informative selection bias, a dynamic MSM [40–43] was fitted using IPW estimation [40, 44, 45] for the purpose of contrasting cumulative risks under the following four TI strategies denoted by d_θ : ‘patient initiates TI at the first time her A1c level reaches or drifts above $\theta\%$ and patient remains on the intensified therapy thereafter’ with $\theta = 7, 7.5, 8$, or 8.5 .

Details of the study design, analytic approach, and results are described elsewhere [46, 47]. In brief, results were consistent with that of ACCORD and ADVANCE and imply that the pattern of results in these trials is applicable to a large population of adults with T2DM treated in routine clinical settings. In particular, findings from the observational study confirmed the benefit of tight glycemic control with respect to the development or progression of albuminuria.

Here, we report on results from secondary analyses of the same observational data to contrast the same four counterfactual survival curves indexed by the TI strategies described earlier for the purpose of evaluating the performance of TMLE compared with IPW estimation. We now formally describe the observational data and the parameter of interest before describing the TMLE approach and its IPW analog.

2.3. Data, parameter of interest, and assumptions

The observed data on each patient in the cohort consist of measurements on exposure, outcome, and confounding variables made at 90-day intervals between study entry and until each patient’s end of follow-up. The time (expressed in units of 90 days) when the patient’s follow-up ends is denoted by \tilde{T} and is defined as the earliest of the time to failure, that is, albuminuria development or progression, denoted by T or the time to a right-censoring event denoted by C . When a patient is right censored, that is, $\tilde{T} = C$, the type of right-censoring event experienced by the patient is recorded and denoted by Γ with possible values of 1, 2, or 3 to represent end of follow-up by administrative end of study, disenrollment from the health plan, or death, respectively. For patients with normoalbuminuria at study entry, that is, a microalbumin-to-creatinine ratio (ACR) of <30, we defined failure as an ACR measurement indicating either microalbuminuria (ACR 30–300) or macroalbuminuria (ACR > 300). For patients with microalbuminuria at study entry, we defined failure as an ACR measurement indicating macroalbuminuria. We thus excluded patients with a baseline ACR measurement missing (5884) or indicating macroalbuminuria (1608), which yielded the sample size $n = 51,179$. The indicator that the follow-up time \tilde{T} is equal to the failure time T is denoted by $\Delta = I(\tilde{T} = T)$. At each time point $t = 0, \dots, \tilde{T}$, the patient’s exposure to an intensified diabetes treatment is represented by the binary variable $A_1(t)$, and the patient’s right-censoring status is denoted by the indicator variable $A_2(t) = I(C \leq t)$. The combination $A(t) = (A_1(t), A_2(t))$ is referred to as the action at time t . At each time point $t = 0, \dots, \tilde{T}$,

covariates (e.g., A1c measurements) are denoted by the multidimensional variable $L(t)$ and defined from measurements that occur before the action at time t , $A(t)$, or are otherwise assumed not to be affected by the actions at time t or thereafter, $(A(t), A(t+1), \dots)$. In particular, the covariates at time t include an outcome measurement denoted by $Y(t)$, that is, $Y(t) \in L(t)$ for $t = 0, \dots, \tilde{T}$. For each time point $t = 0, \dots, \tilde{T} + 1$, the outcome is the indicator of past failure, that is, $Y(t) = I(T \leq t - 1)$. By definition, the outcome is thus 0 for $t = 0, \dots, \tilde{T}$, missing at $t = \tilde{T} + 1$ if $\Delta = 0$, and 1 at $t = \tilde{T} + 1$ if $\Delta = 1$. To simplify notations, we use overbars to denote covariate and exposure histories; for example, a patient's exposure history through time t is denoted by $\bar{A}(t) = (A(0), \dots, A(t))$. Following the MSM framework [40], we approach the observed data in this study as realizations of n independent and identically distributed copies of $O = (\tilde{T}, \Delta, (1 - \Delta)\Gamma, \bar{L}(\tilde{T}), \bar{A}(\tilde{T}), \Delta Y(\tilde{T} + 1))$ denoted by O_i for $i = 1, \dots, n$. The longest observed follow-up time is $\max_{i=1, \dots, n} \tilde{T}_i = 36$ (9 years). Details about the approach implemented for mapping electronic health record data into the coarsened exposure, covariate, and outcome data for each patient were described elsewhere [46, Appendix E].

In this study, we aim to evaluate the effect of dynamic treatment interventions on the cumulative risk of failure at a pre-specified time point t_0 , for example, $t_0 = 11$, to investigate cumulative risks of failure over 3 years. The dynamic treatment interventions of interest correspond to treatment decisions made according to the clinical policies for initiation of an intensified therapy based on the patient's evolving A1c level. These policies denoted by d_θ were described earlier. Formally, these policies are individualized action rules [42] defined as a vector function $d_\theta = (d_\theta(0), \dots, d_\theta(t_0))$ where each function, $d_\theta(t)$ for $t = 0, \dots, t_0$, is a decision rule for determining the action regimen (i.e., a treatment and right-censoring intervention) to be experienced by a patient at time t . A decision rule $d_\theta(t)$ maps the action and covariate history measured up to a given time t to an action regimen at time t : $d_\theta(t) : (\bar{L}(t), \bar{A}(t-1)) \mapsto (a_1(t), a_2(t))$. In this study, the decision rules of interest are defined such that $d_\theta(t)((\bar{L}(t), \bar{A}(t-1)))$ is as follows:

- $(a_1(t), a_2(t)) = (0, 0)$ (i.e., no use of an intensified treatment and no right censoring) if and only if the patient was not previously treated with an intensified therapy (i.e., $\bar{A}(t-1) = 0$) and the A1c level at time t (an element of $L(t)$) was lower than or equal to the threshold θ .
- $(a_1(t), a_2(t)) = (1, 0)$ (i.e., use of an intensified treatment and no right censoring) otherwise.

The parameter of interest denoted by $\psi^{\theta_1, \theta_2}$ is the difference between the cumulative risks at time t_0 associated with any two distinct treatment strategies d_{θ_1} and d_{θ_2} :

$$\psi^{\theta_1, \theta_2} = P(Y_{d_{\theta_1}}(t_0 + 1) = 1) - P(Y_{d_{\theta_2}}(t_0 + 1) = 1).$$

For conciseness, we refer the reader to earlier work [46, Appendices B and D] for a description of the concepts and the counterfactual statistical framework on which relies the definition of this parameter of interest.

Identifiability of this parameter with the observational data described earlier relies on at least three assumptions detailed elsewhere [46, Appendix C]: no unmeasured confounders (and sources of selection bias), positivity, and consistent estimation of the action mechanism. If the aforementioned MSM framework (missing data framework) is not explicitly resting on a more general structural framework through additional explicit assumptions encoded by a causal diagram [48], then an additional assumption referred to as consistency assumption is made [49, 50]. Under these identifiability assumptions, the causal parameter $\psi^{\theta_1, \theta_2}$ can be expressed as a statistical parameter, that is, a parameter of the *observed* data distribution (as opposed to the counterfactual data distribution).

In addition, a more or less flexible non-saturated MSM may be assumed [4, 5, 51–53]. The assumption encoded by such an MSM typically imposes constraints on the survival curves that underlie the definition of the parameter of interest $\psi^{\theta_1, \theta_2}$. In practice, specification of a non-saturated MSM is essentially an arbitrary choice that does not encode real knowledge about the true survival curves of interest. The previous CER analysis of these observational data was based on such an MSM although minimal constraints were actually imposed because the MSM chosen was relatively close to saturation. Approaches to hedge against the bias that would arise from MSM misspecification in practice have been proposed [54] and are still being researched [55].

Alternatively, the MSM may be left nonparametric, that is, no additional assumptions are made (e.g., through specification of a saturated MSM). This is the approach taken here because it reflects the absence of knowledge about the true functional forms of the four survival curves of interest.

3. An alternative to inverse probability weighting estimation

Targeted learning was proposed as a general approach for estimating low-dimensional parameters of the unknown probability distribution that underlies the observed data collected in an observational or randomized study. In the targeted learning literature, the parameter of interest is referred to as the ‘target parameter’. In particular, targeted learning can be used to estimate the target parameter $\psi^{\theta_1, \theta_2}$ under the identifiability assumptions discussed earlier and is then an alternative to IPW estimation of MSM parameters. Similar to other estimation methodologies, estimation with targeted learning is based on a statistical model that restricts the set of possible data-generating distributions. In particular, such a model often imposes constraints on nuisance parameters (e.g., propensity scores (PS)), that is, parameters that are not of interest but are used as the building blocks for deriving an estimate of the target parameter. Contrary to standard practice with other estimation approaches, a tenet of targeted learning is that estimation should be conducted based on ‘honest’ statistical models in practice. By honest, we mean a model that is specified based on *knowledge* as opposed to models that are specified for *convenience*. In most if not all real-world studies, little subject-matter knowledge is available to honestly restrict the set of possible data-generating distributions. Estimation with targeted learning is thus typically based on a nonparametric model, and machine learning is then used for estimating nuisance parameters instead of an arbitrarily specified model that would likely lead to incorrect study findings. The general targeted learning methodology for estimating the target parameter based on machine learning estimates of the nuisance parameters is referred to as the targeted minimum loss-based estimation.[‡] More specifically, targeted learning is the combination of TMLE with a particular machine learning algorithm discussed later and called SL. TMLE is an estimation methodology based on the ‘substitution principle’: the target parameter (denoted by ψ) is expressed as a mapping (denoted by Ψ) of a component (denoted by Q) of the data-generating distribution, that is, $\psi = \Psi(Q)$, and a substitution estimator of ψ may then be defined as $\Psi(Q_n)$ for any given estimator Q_n of Q . TMLE involves two steps for estimating the nuisance parameter Q . First, an initial estimator Q_n of Q is implemented where Q_n is in the parameter space for Q implied by the statistical model for the data-generating distribution. Second, this initial estimator is updated for the purpose of optimizing the bias variance trade-off for the target parameter. The updated estimator of Q is denoted by Q_n^* and is derived based on another component of the data-generating distribution (denoted by g and referred to as the action mechanism). TMLE is defined as estimation with the substitution estimator $\Psi(Q_n^*)$. TMLE is mathematically devised such that $\Psi(Q_n^*)$ is a doubly robust and possibly efficient estimator and such that valid statistical inference can be derived with this estimator even with data-adaptive estimation of the nuisance parameters. Double robustness means that $\Psi(Q_n^*)$ is a consistent regular asymptotically linear estimator of the target parameter as long as at least one of two nuisance parameters, Q or g , is consistently estimated. When both nuisance parameters, Q and g , are estimated consistently, TMLE is efficient in the sense that $\Psi(Q_n^*)$ attains the semiparametric efficiency bound in a model that potentially includes constraints on g , that is, the variance of any regular asymptotically linear estimator of ψ in such a model is greater than or equal to the variance of $\Psi(Q_n^*)$. The mathematical derivation of TMLE for any given observed data and target parameter is based on a well-defined technical road map [21, 22] that is comprehensively described by van der Laan and Rose [16] (e.g., Chapter 5). A brief description of this road map is described by van der Laan and Gruber [20] and applied for estimation of target parameters defined by time-varying interventions such as the parameter $\psi^{\theta_1, \theta_2}$ of interest in this report. Unlike previous application of the technical road map for TMLE, the application of van der Laan and Gruber relies on a novel representation of the target parameter with a mapping Ψ defined by an iterative sequence of conditional expectations of the outcome of interest, which was originally exploited by Bang and Robins [14]. This innovation results in a more practicable TMLE algorithm. In Sections 3.1 and 3.2, we provide an applied description of this TMLE algorithm for estimating $\psi^{\theta_1, \theta_2}$ based on the following new notation.

To simplify the formal description of the TMLE algorithm in the next two sections, we adopt the following new definitions and notation. For any given observed covariate history through time t denoted by $\bar{L}(t)$, the action regimen ($a(0) = d_\theta(0)(L(0))$, $a(1) = d_\theta(1)(\bar{L}(1), a(0))$, ..., $a(t) = d_\theta(t)(\bar{L}(t), \bar{a}(t-1))$) through time t is denoted by $d_\theta(\bar{L}(t))$. For a patient who experiences failure before t_0 (i.e., when $\Delta = 1$ and $\tilde{T} < t_0$), we extend the definition of the patient’s observed data through $t_0 + 1$ by

[‡]The methodology is also referred to as targeted maximum likelihood estimation when it is based on the log-likelihood loss function [19].

including the outcome variables $Y(t+1) = I(T \leq t-1) = 1$ for $\tilde{T} < t \leq t_0$. With this extension, the observed data structure becomes

$$O = (\tilde{T}, \Delta, (1 - \Delta)\Gamma, \bar{L}(\tilde{T}), \bar{A}(\tilde{T}), \Delta\bar{Y}(\tilde{T} + 1, \max(\tilde{T}, t_0) + 1)),$$

where $\Delta\bar{Y}(t, t') = (\Delta Y(t), \dots, \Delta Y(t'))$ with $t \leq t'$. To simplify the following expressions, the outcome $Y(t+1)$ for $\tilde{T} \leq t \leq \max(t_0, \tilde{T})$ when $\Delta = 1$ is also denoted with $L(t+1)$, and the observed data can thus be expressed as

$$O = (\tilde{T}, \Delta, (1 - \Delta)\Gamma, \bar{L}(\tilde{T}), \bar{A}(\tilde{T}), \Delta\bar{L}(\tilde{T} + 1, \max(\tilde{T}, t_0) + 1)).$$

Finally, we define $\check{T}(t) = \min(\tilde{T}, t)$ for $t = 0, \dots, t_0$, and the cumulative counterfactual risk $P(Y_{d_\theta}(t_0 + 1) = 1)$ for any given θ is denoted by γ^θ .

The proposed targeted learning approach for estimating $\psi^{\theta_1, \theta_2}$ consists in estimating each of the two risks γ^{θ_1} and γ^{θ_2} , separately, with the TMLE algorithm described in Section 3.1, which was derived based on the following iterative sequence of conditional expectations for representing γ^θ :

$$\gamma^\theta = E(E[\dots E(E(Y(t_0 + 1) | \mathcal{F}(t_0)) | \mathcal{F}(t_0 - 1)] | \mathcal{F}(t_0 - 2)) \dots | \mathcal{F}(0)])$$

with $\mathcal{F}(t) = (\bar{A}(\check{T}(t)) = d_\theta(\bar{L}(\check{T}(t))), \bar{L}(t))$. An estimate of the risk difference (RD) of interest, $\psi^{\theta_1, \theta_2}$, is then derived by taking the difference between the two resulting estimators denoted by $\gamma_n^{\theta_1, *}$ and $\gamma_n^{\theta_2, *}$, respectively. Inference for the RD is derived based on the influence curve of these two estimators and the delta method [56] as described in Section 3.2.

3.1. Point estimation with targeted minimum loss-based estimation

The following TMLE algorithm was adapted from the algorithm proposed by van der Laan and Gruber [20]. Each of the following steps is implemented sequentially for a given θ to estimate the cumulative risk γ^θ :

- (1) Estimate $P(A(t) = d_\theta(\bar{L}(t)) | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}(t-1) = d_\theta(\bar{L}(t-1)))$ denoted by $g_{A(t)}^\theta$ for $t = 0, \dots, t_0$.

For each t , $g_{A(t)}^\theta$ represents the conditional probability that a patient's exposure and right-censoring status at time t remain concordant with the action implied by the decision rule d_θ given the following: (i) that the patient did not fail before t ; (ii) that the patient's past actions are concordant with action decisions according to rule d_θ ; and (iii) the patient's past observed covariates $\bar{L}(t)$. For this report, several approaches to estimate $g_{A(t)}^\theta$ were implemented, but all are based on separate estimation of each element of the factorization of the action mechanism at time t , that is, $P(A(t) | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}_1(t-1), \bar{A}_2(t-1) = 0)$. The same factorization is typically used to estimate the denominator of the weights in IPW estimation. Specifically, the following probabilities were estimated separately with one of several approaches detailed later:

- PS for TI initiation denoted by μ_1 :

$$P(A_1(t) = 1 | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}_1(t-1) = 0, \bar{A}_2(t) = 0)$$

- PS for TI continuation denoted by μ_2 :

$$P(A_1(t) = 1 | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}_1(t-2), A_1(t-1) = 1, \bar{A}_2(t) = 0)$$

- PS for right censoring by administrative end of study denoted by μ_3 :

$$P(I(A_2(t) = 1, \Gamma = 1) = 1 | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}_1(t-1), \bar{A}_2(t-1) = 0)$$

where $I(\cdot)$ denotes an indicator variable

- PS for right censoring by disenrollment from the health plan denoted by μ_4 :

$$P(I(A_2(t) = 1, \Gamma = 2) = 1 | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}_1(t-1), \bar{A}_2(t-1) = 0, I(A_2(t) = 1, \Gamma = 1) = 0)$$

- PS for right censoring by death denoted by μ_5 :

$$P(I(A_2(t) = 1, \Gamma = 3) = 1 | \bar{L}(t), \bar{Y}(t) = 0, \bar{A}_1(t-1), \bar{A}_2(t-1)) \\ = 0, I(A_2(t) = 1, \Gamma = 1) = 0, I(A_2(t) = 1, \Gamma = 2) = 0)$$

For patients who followed rule d_θ through t (i.e., for whom $\bar{A}(t) = d_\theta(\bar{L}(t))$), an estimate of the nuisance parameter $g_{A(t)}^\theta$ can be derived from estimates of these five PS based on the following equality implied by factorizing the action mechanism at time t using the chain rule:

$$g_{A(t)}^\theta = \left(I(\bar{A}_1(t-1) = 0) \mu_1^{A_1(t)} (1 - \mu_1)^{1-A_1(t)} + I(\bar{A}_1(t-1) = 1) \mu_2^{A_1(t)} (1 - \mu_2)^{1-A_1(t)} \right) \\ \times (1 - \mu_3)(1 - \mu_4)(1 - \mu_5). \quad (1)$$

The estimate of $g_{A(t)}^\theta$ is denoted by $g_{A(t),n}^\theta$.

- (2) Derive an initial estimate of $E(Y(t_0 + 1) | \bar{A}(\check{T}(t_0)) = d_\theta(\bar{L}(\check{T}(t_0))), \bar{L}(t_0))$ denoted by $Q_{L(t_0+1)}^\theta(\bar{L}(t_0))$.

Note that $\bar{L}(t_0 + 1)$ is always defined in the extended observed data structure when $\bar{A}(\check{T}(t_0)) = d_\theta(\bar{L}(\check{T}(t_0)))$ because $\bar{A}(\check{T}(t_0)) = d_\theta(\bar{L}(\check{T}(t_0)))$ implies either of the following: (i) $\check{T}(t_0) = t_0$ and $\check{T}(t_0) < \tilde{T}$ or (ii) $\check{T}(t_0) = \tilde{T} = T$ and $\check{T}(t_0) \leq t_0$ (because $\check{T}(t_0) = \tilde{T} = C$ is not possible when $\bar{A}(\check{T}(t_0)) = d_\theta(\bar{L}(\check{T}(t_0)))$). The conditional expectation $Q_{L(t_0+1)}^\theta(\bar{L}(t_0))$ is thus well defined, and we have

$$Q_{L(t_0+1)}^\theta(\bar{L}(t_0)) = 1 + I(\bar{Y}(t_0) = 0)(E(Y(t_0 + 1) | \bar{A}(t_0) = d_\theta(\bar{L}(t_0)), \bar{L}(t_0), \bar{Y}(t_0) = 0) - 1) \quad (2)$$

This step thus reduces to the estimation of $E(Y(t_0 + 1) | \bar{A}(t_0) = d_\theta(\bar{L}(t_0)), \bar{L}(t_0), \bar{Y}(t_0) = 0)$, that is, the conditional probability that a patient experiences the failure event at time t_0 given the following: (i) that the patient experienced no such event previously and no censoring event before and at t_0 ; (ii) that the patient was continuously treated according to strategy d_θ through t_0 ; and (iii) the patient's covariates through t_0 , $\bar{L}(t_0)$. For this report, several approaches to estimate this probability were implemented and are detailed later. All enforce that the estimate lies in the $[0, 1]$ interval, and all rely solely on data from patients who did not fail before t_0 and who followed rule d_θ through t_0 (i.e., $\bar{Y}(t_0) = 0$ and $\bar{A}(t_0) = d_\theta(\bar{L}(t_0))$). The initial estimate of the nuisance parameter $Q_{L(t_0+1)}^\theta(\bar{L}(t_0))$ is denoted by $Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))$ and is defined as follows: (i) for a patient who did not experience failure before t_0 and who followed rule d_θ through t_0 , $Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))$ is the estimate of the conditional probability just described; and (ii) for a patient who did experience failure before t_0 and who followed rule d_θ until failure, $Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))$ is set to 1 in accordance with equality (2).

- (3) Update the initial estimate of $Q_{L(t_0+1)}^\theta(\bar{L}(t_0))$.

This update is implemented by logistic regression for predicting $Y(t_0 + 1)$ based on an intercept model with an offset variable fitted with weights and using only data from patients who did not fail before t_0 (i.e., $\bar{Y}(t_0) = 0$) and who followed rule d_θ through t_0 (i.e., $\bar{A}(t_0) = d_\theta(\bar{L}(t_0))$). The weight and offset associated with the outcome $Y(t_0 + 1)$ from any patient whose data contribute to this logistic regression are defined as $1/\prod_{t=0}^{t_0} g_{A(t),n}^\theta$ and $\text{logit}(Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))) = \log(Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))/(1 - Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))))$, respectively. The estimate of the intercept resulting from this weighted logistic regression is denoted by ϵ_n . The updated estimate of $Q_{L(t_0+1)}^\theta(\bar{L}(t_0))$ is denoted by $Q_{L(t_0+1),n}^{\theta,*}(\bar{L}(t_0))$ and is defined as follows: (i) for a patient who did not experience failure before t_0 and who followed rule d_θ through t_0 , $Q_{L(t_0+1),n}^{\theta,*}(\bar{L}(t_0))$ is $\text{expit}[\text{logit}(Q_{L(t_0+1),n}^\theta(\bar{L}(t_0))) + \epsilon_n]$ where $\text{expit}(t) = 1/(1 + \exp(-t))$; and (ii) for a patient who did experience failure before t_0 and who followed rule d_θ until failure, $Q_{L(t_0+1),n}^{\theta,*}(\bar{L}(t_0))$ is set to 1 in accordance with equality (2).

- (4) Repeat the following two steps for $k = t_0 - 1, \dots, 0$:

- (a) Derive an initial estimate of $E(Q_{L(k+2)}^\theta(\bar{L}(k+1)) | \bar{A}(\check{T}(k)) = d_\theta(\bar{L}(\check{T}(k))), \bar{L}(k))$ denoted by $Q_{L(k+1)}^\theta(\bar{L}(k))$.

Note that $\bar{L}(k+1)$ is always defined in the extended observed data structure when $\bar{A}(\check{T}(k)) = d_\theta(\bar{L}(\check{T}(k)))$ because $\bar{A}(\check{T}(k)) = d_\theta(\bar{L}(\check{T}(k)))$ implies either of the following: (i) $\check{T}(k) = k$ and $\check{T}(k) < \bar{T}$ or (ii) $\check{T}(k) = \bar{T} = T$ and $\check{T} \leq k$. The conditional expectation $Q_{L(k+1)}^\theta(\bar{L}(k))$ is thus well defined, and we have

$$\begin{aligned} Q_{L(k+1)}^\theta(\bar{L}(k)) &= 1 + I(\bar{Y}(k) = 0) \\ &\times \left(E(Q_{L(k+2)}^\theta(\bar{L}(k+1)) | \bar{A}(k) = d_\theta(\bar{L}(k)), \bar{L}(k), \bar{Y}(k) = 0) - 1 \right) \end{aligned} \quad (3)$$

This step thus reduces to the estimation of

$$E \left(Q_{L(k+2)}^\theta(\bar{L}(k+1)) | \bar{A}(k) = d_\theta(\bar{L}(k)), \bar{L}(k), \bar{Y}(k) = 0 \right) \quad (4)$$

that is, the conditional expectation of the continuous measure $Q_{L(k+2)}^\theta(\bar{L}(k+1))$ (itself a conditional expectation between 0 and 1) characterizing a patient at time $k+1$ given the following: (i) that the patient did not experience failure before k and no censoring event before and at k ; (ii) that the patient was continuously treated according to strategy d_θ through k ; and (iii) the patient's baseline and past time-varying covariates through k , $\bar{L}(k)$. For this report, several approaches to estimate this expectation were implemented and are detailed later. All enforce that the estimate lies in the $[0, 1]$ interval, and all rely solely on data from patients who did not fail before k and who followed rule d_θ through k (i.e., $\bar{Y}(k) = 0$ and $\bar{A}(k) = d_\theta(\bar{L}(k))$). In particular, the datum $Q_{L(k+2),n}^{\theta,*}(\bar{L}(k+1))$ is needed for each of these patients. Among them, some may have followed rule d_θ through $k+1$, and others may only have followed rule d_θ through k . For the first group of patients, we already computed an estimate $Q_{L(k+2),n}^{\theta,*}(\bar{L}(k+1))$ in the latest 'update step' while for the second group of patients, such estimates need to be computed here by extrapolation, that is, using the same protocol employed in the latest 'update step' as if these patients also followed rule d_θ at time $k+1$. The initial estimate of the nuisance parameter $Q_{L(k+1)}^\theta(\bar{L}(k))$ is denoted by $Q_{L(k+1),n}^\theta(\bar{L}(k))$ and is defined as follows: (i) for a patient who did not experience failure before k and who followed rule d_θ through k , $Q_{L(k+1),n}^\theta(\bar{L}(k))$ is the estimate of conditional expectation (4); and (ii) for a patient who did experience failure before k and who followed rule d_θ until failure, $Q_{L(k+1),n}^\theta(\bar{L}(k))$ is set to 1 in accordance with equality (3).

- (b) Update the initial estimate of $Q_{L(k+1)}^\theta(\bar{L}(k))$.

This update is implemented by logistic regression for predicting $Q_{L(k+2)}^\theta(\bar{L}(k+1))$ based on an intercept model with an offset variable fitted with weights and using only data from patients who did not fail before k (i.e., $\bar{Y}(k) = 0$) and who followed rule d_θ through k (i.e., $\bar{A}(k) = d_\theta(\bar{L}(k))$). The weight and offset associated with the outcome $Q_{L(k+2),n}^{\theta,*}(\bar{L}(k+1))$ from any patient whose data contribute to this logistic regression are defined as $1/\prod_{t=0}^k g_{A(t),n}^\theta$ and $\text{logit}(Q_{L(k+1),n}^\theta(\bar{L}(k))) = \log(Q_{L(k+1),n}^\theta(\bar{L}(k))/(1 - Q_{L(k+1),n}^\theta(\bar{L}(k))))$, respectively. The estimate of the intercept resulting from this weighted logistic regression is denoted by ϵ_n . The updated estimate of $Q_{L(k+1)}^\theta(\bar{L}(k))$ is denoted by $Q_{L(k+1),n}^{\theta,*}(\bar{L}(k))$ and is defined as follows: (i) for a patient who did not experience failure before k and who followed rule d_θ through k , $Q_{L(k+1),n}^{\theta,*}(\bar{L}(k))$ is $\text{expit}[\text{logit}(Q_{L(k+1),n}^\theta(\bar{L}(k))) + \epsilon_n]$; and (ii) for a patient who did experience failure before k and who followed rule d_θ until failure, $Q_{L(k+1),n}^{\theta,*}(\bar{L}(k))$ is set to 1 in accordance with equality (3).

- (5) Derive the estimate of $E(Q_{L(1)}^\theta(L(0)))$ denoted by $Q_{L(0)}^\theta$.

For patients who followed rule d_θ at time 0, we already computed an estimate $Q_{L(1),n}^{\theta,*}(L(0))$ in the latest 'update step'. For all other patients, an estimate $Q_{L(1),n}^{\theta,*}(L(0))$ is computed here by extrapolation, that is, using the same protocol employed in the latest 'update step' as if these patients also followed rule d_θ at time 0. Thus, an estimate $Q_{L(1),n}^{\theta,*}(L(0))$ is now available for all n patients in the cohort. The average of these estimates is an estimate of $Q_{L(0)}^\theta$ denoted by $Q_{L(0),n}^{\theta,*}$:

$$Q_{L(0),n}^{\theta,*} = \frac{1}{n} \sum_{i=1}^n Q_{L(1),n}^{\theta,*}(L_i(0))$$

This estimate $Q_{L(0),n}^{\theta,*}$ is the TMLE point estimate of the counterfactual cumulative risk of interest γ^θ , and we thus also denote it by $\gamma_n^{\theta,*}$.

From the TMLE point estimates $\gamma_n^{\theta_1,*}$ and $\gamma_n^{\theta_2,*}$ obtained by applying twice the preceding five steps with, first, $\theta = \theta_1$ and, second, $\theta = \theta_2$, we derived a point estimate for the parameter of interest ψ^{θ_1,θ_2} . This estimate is denoted by $\psi_n^{\theta_1,\theta_2,*}$, and we have $\psi_n^{\theta_1,\theta_2,*} = \gamma_n^{\theta_1,*} - \gamma_n^{\theta_2,*}$. Note that the preceding algorithm can also be repeated for a continuous sequence of time points starting at $t_0 = 0$. The resulting estimates of the counterfactual cumulative risks can then be mapped into an estimate of the corresponding counterfactual survival curve using the link $S_{d_\theta}(t) = 1 - P(Y_{d_\theta}(t+1) = 1)$, where $S_{d_\theta}(t) = P(T_{d_\theta} > t)$ denotes the probability of survival at time t . The estimate of $S_{d_\theta}(t)$ obtained with this approach is denoted by $S_{d_\theta,n}^*(t)$.

To implement the preceding TMLE algorithm, we need to specify estimation approaches for two vectors of nuisance parameters denoted by g^θ and Q^θ . The nuisance parameter g^θ corresponds with the estimands in step 1, that is, $g_{A(t)}^\theta$ for $t = 0, \dots, t_0$. The nuisance parameter Q^θ corresponds with the estimands in all other steps, that is, $Q_{L(t+1)}^\theta(\bar{L}(t))$ for $t = 0, \dots, t_0$. The estimator $\gamma_n^{\theta,*}$ is doubly robust in the sense that it is a consistent estimator of the true cumulative risk γ^θ if either the estimator of the nuisance parameter g^θ is a consistent estimator of the true g^θ or if the initial estimator of the nuisance parameter Q^θ is a consistent estimator of the true Q^θ . In addition, $\gamma_n^{\theta,*}$ is efficient if both estimators of the nuisance parameters are consistent.

Given that IPW estimation also relies on an estimate of the nuisance parameter g^θ , we initially evaluated TMLE using the same estimation approach for g^θ that had been implemented in a previous work [46]. The approach is based on mapping (1) that links the nuisance parameter g^θ to the five PS μ_1, \dots, μ_5 . Data were pooled for all time points $t = 0, \dots, 36$ to fit a separate main-term logistic model for estimating each of the three PS for right censoring (μ_3, μ_4, μ_5) and the PS for TI continuation (μ_2). Data were also pooled for all time points $t > 0$ to fit a single main-term logistic model for estimating the PS for TI initiation after $t = 0$ (i.e., μ_1 for $t > 0$). A separate main-term logistic model was fitted for estimating the PS for TI initiation at $t = 0$ (i.e., μ_1 for $t = 0$). By ‘main-term logistic model’, we mean a logistic model with only main terms for each explanatory variable considered (i.e., no interaction terms between explanatory variables). The explanatory variables considered were all time-independent covariates and the last measurement of time-varying covariates. In addition, exposure to TI in the last period was included as an explanatory variable for the three PS for right censoring, and the latest change in A1c was included as an explanatory variable for estimating all PS. All pooled models over time also included the variable indexing the 90-day follow-up intervals (i.e., t) as an explanatory variable.

For deriving the initial estimate of the nuisance parameter Q^θ , we relied on the machine learning algorithm ‘DSA’ [57, 58]. The DSA implements data-adaptive estimator selection based on cross-validation. The candidate estimators considered were restricted to main-term logistic models of different sizes with the following candidate explanatory variables: all time-independent covariates, the last measurement of time-varying covariates, and the latest change in A1c. To alleviate computing time, the DSA algorithm was implemented with a single fivefold cross-validation split, without deletion and substitution moves, and with a maximum model size of 10 explanatory variables.

The resulting estimates of the four counterfactual survival curves $S_{d_\theta,n}^*(t)$ for $\theta = 7, 7.5, 8, 8.5$ and $t = 0, \dots, 15$ (4 years of follow-up) are displayed in Figure 1. The corresponding estimates of the six distinct RDs $\psi_n^{\theta_1,\theta_2,*}$ for $t_0 = 11$, that is, the difference of counterfactual cumulative risks over 3 years, are displayed in Table I.

Note that while the TMLE algorithm just described may appear complex, it essentially involves the implementation of a sequence of standard regression steps to fit logistic models and derive predicted values from these models. Implementation with standard statistical software is thus relatively trivial as reflected by the R programming code in Appendix A.1 and the corresponding computing time needed to derive estimates $\psi_n^{\theta_1,\theta_2,*}$ in R version 2.13.0 [59]. When we exclude the time needed to derive the estimate of the nuisance parameter g^θ and the initial estimate of the nuisance parameter Q^θ , the completion of the remaining steps of the TMLE algorithm was obtained in about 1 min. The overall computing time

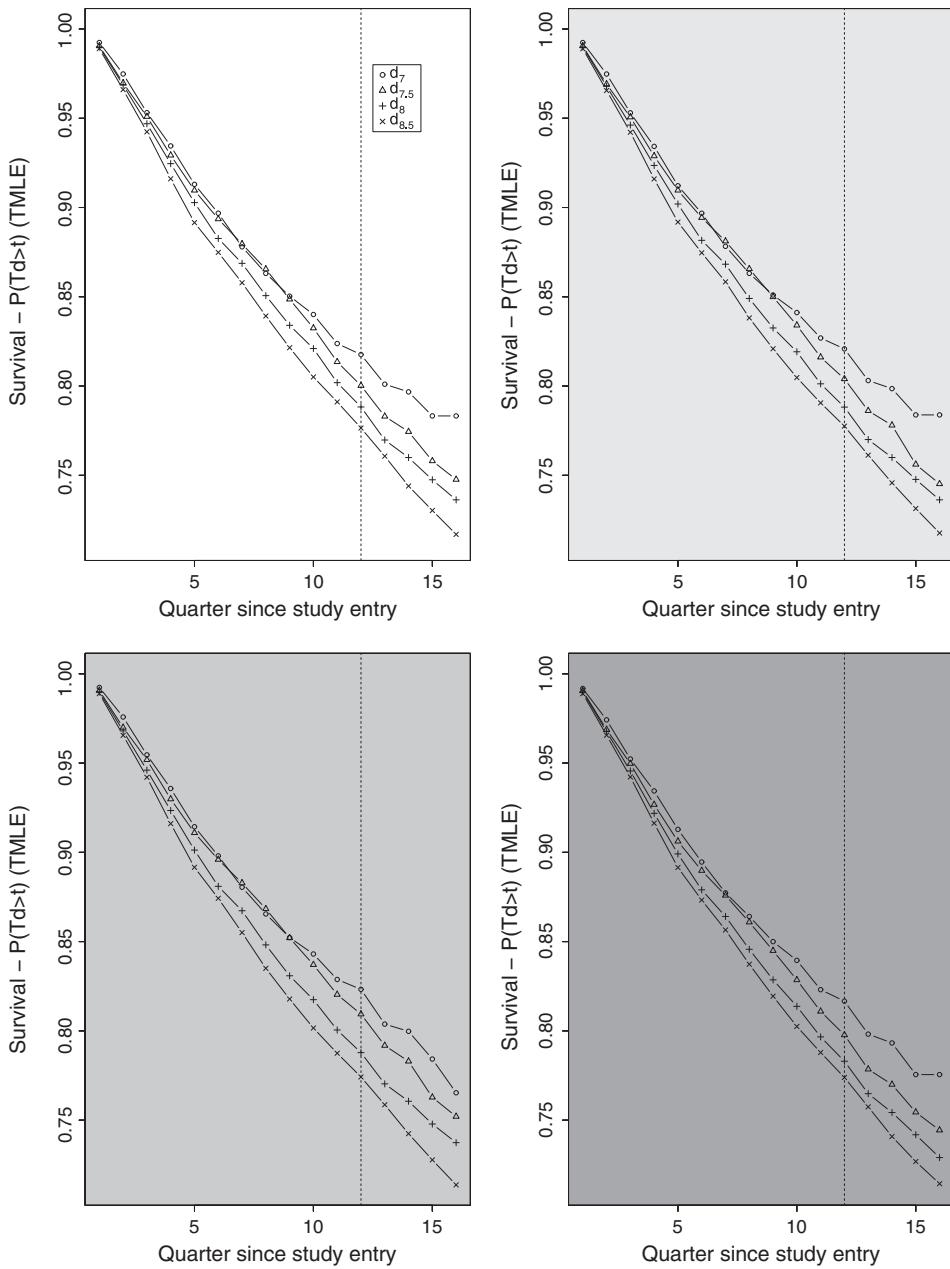


Figure 1. Each plot represents targeted minimum loss-based estimation (TMLE) estimates over 16 quarters of the four counterfactual survival curves corresponding with the four treatment intensification initiation strategies d_θ with $\theta = 7, 7.5, 8, 8.5$. The plots located at the top left, top right, bottom left, and bottom right are obtained based on the estimates g_n^θ , $g_{n,t}^\theta$, $g_{n,t,x}^\theta$, and $g_{n,t,SL}^\theta$ of the nuisance parameter g^θ , respectively.

to derive the estimate $\psi_n^{\theta_1, \theta_2, *}$ was however about 40 min because of the computing burden imposed by the DSA algorithm. This computing time can thus be greatly shortened with the selection of a faster machine learning algorithm instead of the DSA or through the arbitrary specification of logistic models for the different components of the nuisance parameter Q^θ (as was performed for estimating the nuisance parameter g^θ). Before evaluating the performance of TMLE by comparison with IPW estimation, we now discuss approaches for deriving inference with TMLE.

3.2. Inference with targeted minimum loss-based estimation

The estimator $\gamma_n^{\theta, *}$ defined by the preceding TMLE algorithm is asymptotically linear with the influence curve denoted by $IC_\theta^*(O | g^\theta, Q^\theta)$ and defined by

Table I. Comparison of inferences from untruncated TMLE and IPW estimation of the six RDs at 3 years (12 quarters) based on the four approaches to estimate the nuisance parameter g_θ^* .

θ_1	θ_2	g^θ	TMLE			IPW estimation			Relative efficiency	
			$\psi_n^{\theta_1, \theta_2, *}$	$\psi_n^{\theta_1, \theta_2, *, -}$	p^*	RSE*	$\psi_n^{\theta_1, \theta_2}$	$\psi_n^{\theta_1, \theta_2, +}$	p	RSE
8.5	8	g_n^θ	0.01118	-5e-03	0.0286	0.167	1.52	0.0109	-3e-04	0.022
8.5	7.5	g_n^θ	0.0237	-2.3e-03	0.0498	0.074	1.58	0.0212	4.1e-03	0.0382
8.5	7	g_n^θ	0.0411	9.1e-03	0.0732	0.012	1.23	0.0387	0.0122	0.0652
8	7.5	g_n^θ	0.0119	-0.0117	0.0356	0.323	1.61	0.0103	-5e-03	0.0256
8	7	g_n^θ	0.0293	-4.8e-03	0.0635	0.092	1.29	0.0278	8e-04	0.0549
7.5	7	g_n^θ	0.0174	-0.0165	0.0513	0.315	1.33	0.0175	-8.5e-03	0.0435
8.5	8	$g_{n,t}^\theta$	0.0107	-3e-03	0.0243	0.127	1.31	9.9e-03	-9e-04	0.0207
8.5	7.5	$g_{n,t}^\theta$	0.0264	6.9e-03	0.046	8e-03	1.31	0.025	9.6e-03	0.0404
8.5	7	$g_{n,t}^\theta$	0.0433	0.0192	0.0674	0	1	0.0418	0.0172	0.0664
8	7.5	$g_{n,t}^\theta$	0.0158	-2.1e-03	0.0337	0.084	1.32	0.0151	1.2e-03	0.029
8	7	$g_{n,t}^\theta$	0.0326	6.7e-03	0.0586	0.014	1.05	0.0319	6.7e-03	0.0571
7.5	7	$g_{n,t}^\theta$	0.0168	-7.9e-03	0.0416	0.182	1.08	0.0168	-6.7e-03	0.0403
8.5	8	$g_{n,t,\times}^\theta$	0.0136	1.2e-03	0.0261	0.032	1.16	0.0129	2.1e-03	0.0237
8.5	7.5	$g_{n,t,\times}^\theta$	0.0352	0.0171	0.0533	0	1.2	0.0337	0.0183	0.0491
8.5	7	$g_{n,t,\times}^\theta$	0.0491	0.0245	0.0737	0	0.98	0.0483	0.0229	0.0737
8	7.5	$g_{n,t,\times}^\theta$	0.0216	5.2e-03	0.038	1e-02	1.23	0.0209	7.3e-03	0.0345
8	7	$g_{n,t,\times}^\theta$	0.0355	0.0102	0.0608	6e-03	1	0.0354	1e-02	0.0608
7.5	7	$g_{n,t,\times}^\theta$	0.0139	-0.0102	0.038	0.259	1.02	0.0146	-9.2e-03	0.0383
8.5	8	$g_n^{\theta, f}$	9.1e-03	1.4e-03	0.0168	0.021	0.99	8e-03	1e-04	0.0159
8.5	7.5	$g_n^{\theta, f, SL}$	0.0238	0.0102	0.0374	1e-03	1	0.0216	7.7e-03	0.0356
8.5	7	$g_n^{\theta, f, SL}$	0.0427	0.0194	0.0661	0	0.97	0.041	0.0166	0.0655
8	7.5	$g_n^{\theta, f, SL}$	0.0147	2.3e-03	0.0271	2e-02	0.99	0.0136	1e-03	0.0263
8	7	$g_n^{\theta, f, SL}$	0.0336	0.0104	0.0569	5e-03	0.97	0.033	8.6e-03	0.0574
7.5	7	$g_n^{\theta, f, SL}$	0.0189	-2.5e-03	0.0403	0.083	0.96	0.0194	-3e-03	0.0418

Estimates based on TMLE versus IPW estimation are differentiated by the superscript * notation.

$$IC_{\theta}^*(O | g^{\theta}, Q^{\theta}) = \sum_{t=0}^{t_0+1} D_{\theta,t}^*(O | g^{\theta}, Q^{\theta}) \text{ with} \\ D_{\theta,t}^*(O | g^{\theta}, Q^{\theta}) = \frac{I(\bar{A}(\check{T}(t-1)) = d_{\theta}(\bar{L}(\check{T}(t-1))))}{\prod_{j=0}^{\check{T}(t-1)} g_{A(j)}^{\theta}} (Q_{L(t+1)}^{\theta} - Q_{L(t)}^{\theta}) \quad (5)$$

where $Q_{L(t_0+2)}^{\theta} = Y(t_0+1)$ and $I(\bar{A}(\check{T}(t-1)) = d_{\theta}(\bar{L}(\check{T}(t-1))))/\prod_{j=0}^{\check{T}(t-1)} g_{A(j)}^{\theta}$ is nil at $t = 0$ [20].

Note that $D_{\theta,t}^*(O | g^{\theta}, Q^{\theta}) = 0$ for all t such that either of the following happens: (i) $\check{T} = C$ and $C + 1 \leq t \leq t_0 + 1$ because we then have $I(\bar{A}(\check{T}(t-1)) = d_{\theta}(\bar{L}(\check{T}(t-1)))) = 0$ or (ii) $\check{T} = T$ and $T + 1 < t \leq t_0 + 1$ because we then have $Q_{L(t+1)}^{\theta} - Q_{L(t)}^{\theta} = 0$.

From the delta method, the estimator $\psi_n^{\theta_1, \theta_2, *}$ is thus asymptotically linear with the influence curve $IC_{\theta_1, \theta_2}^*(O | g^{\theta_1}, Q^{\theta_1}, g^{\theta_2}, Q^{\theta_2}) = IC_{\theta_1}^*(O | g^{\theta_1}, Q^{\theta_1}) - IC_{\theta_2}^*(O | g^{\theta_2}, Q^{\theta_2})$, that is,

$$\psi_n^{\theta_1, \theta_2, *} - \psi^{\theta_1, \theta_2} = \frac{1}{n} \sum_{i=1}^n IC_{\theta_1, \theta_2}^*(O_i | g^{\theta_1}, Q^{\theta_1}, g^{\theta_2}, Q^{\theta_2}) + o\left(\frac{1}{\sqrt{n}}\right)$$

Under the assumption that $g_n^{\theta_1}$ and $g_n^{\theta_2}$ are consistent estimators, a conservative estimate of the asymptotic SE of $\psi_n^{\theta_1, \theta_2, *}$ is given by

$$\sigma_n^{\theta_1, \theta_2, *} = \sqrt{\frac{1}{n^2} \sum_{i=1}^n \left[IC_{\theta_1, \theta_2}^*(O_i | g_n^{\theta_1}, Q_n^{\theta_1, *}, g_n^{\theta_2}, Q_n^{\theta_2, *}) \right]^2} \quad (6)$$

where $g_n^{\theta} = (g_{A(0),n}^{\theta}, \dots, g_{A(t_0),n}^{\theta})$ is the vector of estimates obtained in step 1 of the TMLE algorithm and $Q_n^{\theta, *} = (Q_{L(0),n}^{\theta, *}, \dots, Q_{L(t_0+1),n}^{\theta, *})$ is the vector of updated estimates obtained at each ‘update step’ of the TMLE algorithm. Thus, computation of the estimated SE of the estimator $\psi_n^{\theta_1, \theta_2, *}$ with formula (6) does not add significant computing time to the TMLE approach because, as shown by the R programming code in Appendix A.2, it is based on by-products (g_n^{θ} and $Q_n^{\theta, *}$) of the algorithm for deriving the point estimate.

For each of the six RDs of interest, we can thus compute the lower and upper bounds of the 95% confidence interval (CI) and the p -value associated with the two-sided test of the null hypothesis ($H_0 : \psi^{\theta_1, \theta_2} = 0$) as follows:

$$P\left(\underbrace{\psi_n^{\theta_1, \theta_2, *} - z_{0.025}\sigma_n^{\theta_1, \theta_2, *}}_{\text{denoted by } \psi_n^{\theta_1, \theta_2, *, -}} \leq \psi^{\theta_1, \theta_2} \leq \underbrace{\psi_n^{\theta_1, \theta_2, *} + z_{0.025}\sigma_n^{\theta_1, \theta_2, *}}_{\text{denoted by } \psi_n^{\theta_1, \theta_2, *, +}}\right) = 0.95 \text{ and } 2\Phi\left(-\left|\frac{\psi_n^{\theta_1, \theta_2, *}}{\sigma_n^{\theta_1, \theta_2, *}}\right|\right) \quad p\text{-value denoted by } p^* \quad (7)$$

where $z_{0.025} = \Phi^{-1}(0.975)$ and Φ is the cumulative distribution function of the standard normal distribution.

The estimates of the SEs, CIs, and p -values derived analytically from expressions (6) and (7) for each of the six distinct RDs $\psi^{\theta_1, \theta_2}$ are displayed in Table I. To assess the performance of estimator (6) in evaluating the variability of $\psi_n^{\theta_1, \theta_2, *}$, we also evaluated the variability of $\psi_n^{\theta_1, \theta_2, *}$ based on 10,000 bootstrap samples. For a fair comparison between both estimates of TMLE variability, the point estimates of $\psi^{\theta_1, \theta_2}$ were derived on each bootstrap sample using the same original estimated nuisance parameters $g_n^{\theta_1}$ and $g_n^{\theta_2}$ (i.e., the five PS models in step 1 were not refitted on each bootstrap sample) because estimator (6) is only consistent for estimating the SE of $\psi_n^{\theta_1, \theta_2, *}$ when the nuisance parameter g^{θ} is known. In Table I, the ratios (denoted by RSE*) of the estimates of the SE based on the influence curve over that derived from the bootstrap indicate important overestimation (by up to 61%) of the TMLE SE with formula (6). Given that the performance of the SE estimator (6) relies on correct estimation of the nuisance parameters g^{θ} , we hypothesized that the poor performance of estimator (6) could be the result

of misspecification of the logistic models for the PS on which are based the current estimates of the nuisance parameters g^θ .

Thus, in addition to the first approach described in Section 3.1, we also implemented the TMLE algorithm for estimating the four survival curves $S_{d_\theta}(t)$ and the six RDs $\psi^{\theta_1, \theta_2}$ with three alternate approaches to estimate the nuisance parameter g^θ . These approaches numbered 1 through 4 are progressively more flexible, that is, nonparametric:

- Approach 1: This is the approach based on the six main-term logistic models described in Section 3.1. Note that five of these models are based on data pooled over time.
- Approach 2: For each time point t separately, five main-term logistic models were fitted to estimate each of the five PS.
- Approach 3: The logistic models from approach 2 were all modified to include interactions terms between explanatory variables. The interaction terms added to each logistic model were selected using the following algorithm: 105 two-way interaction terms were computed based on the 15 explanatory variables that were the most associated (smallest p -value) with the PS dependent variable (denoted by Z) in a univariate logistic regression. For each of these 105 terms, a logistic regression of Z on the interaction term and the two main terms that define the interaction term was implemented. The p -values p associated with the interaction terms in these 105 regressions were used to identify all interaction terms with $p < 0.05$. If more than 50 interaction terms met this criterion, only the 50 terms with the smallest p were selected and added to the main-term logistic model for the PS.
- Approach 4: The parametric models adopted for estimating g^θ in approaches 1–3 do not reflect true subject-matter knowledge about the five PS. To avoid erroneous inference [12, 60] due to arbitrary model specifications, data-adaptive estimation of the nuisance parameter g^θ may be implemented in practice [61, 62], but consistent estimation then relies on judicious selection of a machine learning algorithm also known as ‘learner’. Several learners are potential candidates for estimating the five PS (e.g., [57, 63–71]). Akin to the selection of a parametric model, the selection of a learner does not typically reflect real subject-matter knowledge about the relative suitability of the different learners available, as ‘in practice it is generally impossible to know a priori which learner will perform best for a given prediction problem and data set’ [17]. To hedge against erroneous inference due to arbitrary selection of a learner, SL [17] may be implemented to combine predicted values from a library of various candidate learners (which includes the arbitrary learner that would have been guessed otherwise) through a weighted average. The selection of the optimal combination of the candidate learners is based on cross-validation [72–75] to protect against overfitting such that the resulting learner (called ‘super learner’) performs asymptotically as well (in terms of mean error) or better than any of the candidate learners considered. If the arbitrary learners that would have been guessed are based on a parametric model and happen to be correct, then using SL instead of the correctly guessed learner only comes at a price of limited increase in prediction variability.

For each time point t separately, five super learners were implemented to estimate each of the five PS based on 10 candidate learners: (i) five learners[§] defined by logistic models with only main terms for the most predictive explanatory variables identified[¶] by a significant p -value in univariate regressions with five significance levels ($\alpha = 1e-30, 1e-10, 1e-5, 0.1$, and 1); and (ii) five polyphasic regression learners^{||} based on the most predictive explanatory variables identified by a significant p -value in univariate regressions with the same five significance levels.

Note that unlike the computing time for the first three approaches, which is measured in minutes, approach 4 based on SL is computing intensive: approximately 7, 1, 4, 7, and 10 h were needed to derive the five sets of super learners for TI initiation, TI continuation, censoring by administrative end of study, censoring by disenrollment from the health plan, and censoring by death, respectively. To simplify the notation, we denote the estimate of g^θ obtained with approaches 1–4 by g_n^θ , $g_{n,t}^\theta$, $g_{n,t,\times}^\theta$, and $g_{n,t,SL}^\theta$,

[§] Implemented by the `SL.glm` routine available in the `SuperLearner` R package [76].

[¶] Using the template screening routine `screen.glmP` available in the `SuperLearner` R package.

^{||} Implemented by the `SL.polyclass` routine given in [77, Appendix]. This routine implements the polyclass learner [69] based on the Bayesian information criterion as the model selection criterion. To improve computing speed, this learner was favored over the `SL.polymars` routine that is available by default in the `SuperLearner` R package but that relies on cross-validation for model selection.

respectively. The TMLE of the four survival curves $S_{d_\theta}(t)$ and the six RDs $\psi^{\theta_1, \theta_2}$ based on these four estimates of g^θ are displayed in Table I and Figure 1.

In Table I, it is clear that the ratios (RSE*) of the estimates of the TMLE SE based on the influence curve over that derived from the bootstrap get progressively closer to 1 as the approach used to estimate g^θ becomes more nonparametric. The desired ratios of 1 are approximately reached with SL estimation of the action mechanism, that is, with $g_{n,t,SL}^\theta$. These results are consistent with our earlier hypothesis for explaining the initial poor performance of the analytic estimator of the SE associated with the TMLE estimator $\psi_n^{\theta_1, \theta_2, *}$ that is based on the estimate g_n^θ . They suggest the following: (1) the logistic models used in approach 1 to derive the estimate g_n^θ were misspecified; and (2) SL was successfully permitted to hedge against such misspecification by correcting for the bias in estimating g^θ with approach 1. Unlike the clear sensitivity of the estimates of TMLE variability to the choice of estimator for g^θ (Table I), Figure 1 suggests however that the TMLE point estimates are much less sensitive to the approach taken for estimating g^θ because the plots of survival curves associated with approaches 1–4 are relatively stable.

To evaluate the performance in time-dependent confounding and selection bias adjustment with the TMLE algorithm, we now compare the inferences obtained with TMLE with that obtained with IPW estimation in the following.

3.3. Comparison to inverse probability weighting estimation

In a previous work [46], stabilized IPW estimation of the same four survival curves and six RDs was implemented based on a parametric dynamic MSM for the four discrete-time hazards. Estimates of the hazards were subsequently mapped into estimates of each of the four corresponding counterfactual survival curves from which inferences about RDs were derived.

Because these IPW estimates were derived in a previous analysis based on additional modeling assumptions encoded by a non-saturated MSM, direct comparison with the TMLE estimates in this report is not optimal. For a fair comparison, we implemented the same general stabilized IPW estimation approach based on the same four approaches for estimating the nuisance parameter g^θ but using the following saturated MSM, which is equivalent to a nonparametric MSM:

$$\begin{aligned} \text{logit} (P(Y_{d_\theta}(t+1) = 1 | Y_{d_\theta}(t) = 0)) \\ = \sum_{\theta' \in \{7, 7.5, 8, 8.5\}} \sum_{j=0}^{36} \beta_j^{\theta'} I(\theta = \theta', t = j) \text{ for } \theta \in \{7, 7.5, 8, 8.5\} \text{ and } t = 0, \dots, 36 \end{aligned}$$

Another difference with the IPW estimation implemented in a previous work is that we do not assume that right censoring due to the administrative end of study is uninformative in this report. For simplicity, this assumption had been made in the earlier analyses even though administrative end of study could potentially result in selection bias because of the cohort being open. When one assumes that some right-censoring events are not informative, IPW estimation can be simplified by ignoring the corresponding conditional probabilities of censoring in the calculation of stabilized weights because weight stabilization results in cancellation of such probabilities in the numerator and denominator of the weights. Because weight stabilization is not possible in TMLE of the cumulative risks γ^θ , estimation of the conditional probability of right censoring due to administrative end of study is needed for TMLE implementation even if such events can be assumed to be uninformative. For this reason, we relaxed the assumption of uninformative censoring due to administrative end of study when implementing TMLE. We thus also relaxed this assumption when implementing IPW estimation to enable a fair comparison of the two approaches.

The IPW estimator $\beta_{t,n}^\theta$ of each coefficient β_t^θ of the saturated MSM can be derived by a single standard weighted regression as was performed in the aforementioned previous work. Equivalently, each $\beta_{t,n}^\theta$ can be derived separately by solving the estimating equation associated with the following IPW estimating function for the discrete-time hazard under rule d_θ at time t :

$$D(O | \alpha_t^\theta) = I(Y(t) = 0)I(\bar{A}(t) = d_\theta(\bar{L}(t))) \\ \times \frac{\prod_{j=0}^t P(A(j) = d_\theta(\bar{L}(j)) | Y(j) = 0, \bar{A}(j-1) = d_\theta(\bar{L}_i(j-1)))}{\prod_{j=0}^t g_{A(j)}^\theta} (Y(t+1) - \alpha_t^\theta)$$

where the counterfactual discrete-time hazard $P(Y_{d_\theta}(t+1) = 1 | Y_{d_\theta}(t) = 0)$ is denoted by α_t^θ . The resulting estimator denoted by $\alpha_{t,n}^\theta$ is defined as

$$\alpha_{t,n}^\theta = \frac{\sum_{i=1}^n I(Y_i(t)=0)I(\bar{A}_i(t) = d_\theta(\bar{L}_i(t))) \frac{\prod_{j=0}^t P(A_i(j)=d_\theta(\bar{L}_i(j))|Y(j)=0, \bar{A}_i(j-1)=d_\theta(\bar{L}_i(j-1)))}{\prod_{j=0}^t g_{A_i(j)}^\theta} Y_i(t+1)}{\sum_{i=1}^n I(Y_i(t)=0)I(\bar{A}_i(t) = d_\theta(\bar{L}_i(t))) \frac{\prod_{j=0}^t P(A_i(j)=d_\theta(\bar{L}_i(j))|Y(j)=0, \bar{A}_i(j-1)=d_\theta(\bar{L}_i(j-1)))}{\prod_{j=0}^t g_{A_i(j)}^\theta}}$$

and we have $\beta_{t,n}^\theta = \log(\alpha_{t,n}^\theta)$. Computing time is greatly shortened with this second approach for deriving $\beta_{t,n}^\theta$.

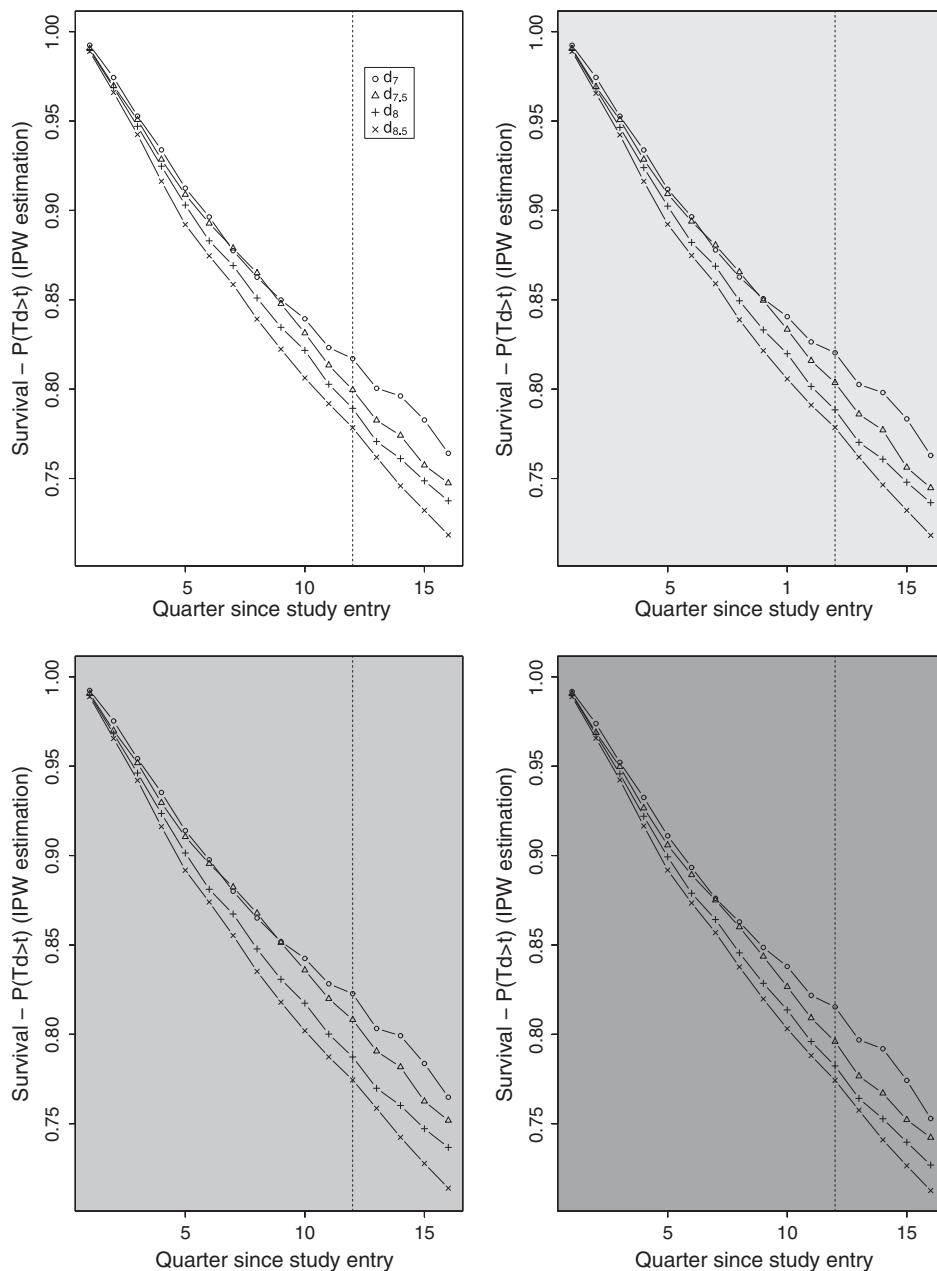


Figure 2. Each plot represents inverse probability weighting (IPW) estimates over 16 quarters of the four counterfactual survival curves corresponding with the four treatment intensification initiation strategies d_θ with $\theta = 7, 7.5, 8, 8.5$. The plots located at the top left, top right, bottom left, and bottom right are obtained based on the estimates $g_n^\theta, g_{n,t}^\theta, g_{n,t,\times}^\theta$, and $g_{n,t,SL}^\theta$ of the nuisance parameter g^θ , respectively.

Note that unlike TMLE, which is doubly robust, IPW estimation relies on consistent estimation of the nuisance parameter g^θ . In this report, however, we aim to evaluate the performance of both approaches under consistent estimation of the nuisance parameter g^θ . Table I and Figure 2 display the results of IPW estimation under the four approaches considered for estimating g^θ . In addition, Figure 3 displays the results from a crude analysis that consists in fitting a saturated logistic model for the discrete-time hazards without weights, that is, without adjustment for time-dependent confounding and selection bias.

A comparison of the crude and IPW estimates of the survival curves on Figures 2 and 3 clearly demonstrates successful adjustment for time-dependent confounding and selection bias with the IPW approach. Whichever the approach adopted for estimating g^θ , the IPW estimates indicate an early separation and consistent ordering of the four survival curves, suggesting an increasing beneficial effect of more aggressive therapy initiation rules (i.e., of rules indexed by decreasing A1c thresholds). These results are consistent with that of the ACCORD and ADVANCE randomized trials. Successful performance in bias adjustment with the TMLE approach is illustrated in Figure 1, which indicates the same separation of the four survival curves. The estimates of the survival curves obtained by IPW estimation are visually almost identical to that obtained by TMLE.

The stability of the survival curves on Figures 1 and 2 suggests that estimation bias for g^θ with the first three approaches is relatively minor with respect to its impact on confounding and selection bias adjustment with both TMLE and IPW estimations. It is of interest to note that while Table I indicates that the analytic estimate of the TMLE variability is largely affected ($RSE^* > 1$ with g_n^θ , $g_{n,t}^\theta$, and $g_{n,t,x}^\theta$) by such minor bias in estimation of g^θ , the analytic estimates of IPW estimation variability remain largely unaffected by such bias ($RSE \approx 1$, whichever the approach for estimating g^θ).

Table I also indicates that the SE of the IPW estimators (denoted by $\sigma_n^{\theta_1, \theta_2}$) decreases as the approach taken for estimating g^θ becomes more flexible. This gain in estimation efficiency is explained by the decrease in the proportion of large weights from progressively more flexible approaches as shown in Table II. In fact, none of the stabilized inverse probability (IP) weights derived from SL are greater than 30. This is quite remarkable given the common intuition that data-adaptive estimation may not be desirable for practical implementation of IPW estimation for fear to reveal violations of the positivity assumption. Intuitively, estimation of the IP weights based on arbitrarily specified parametric models

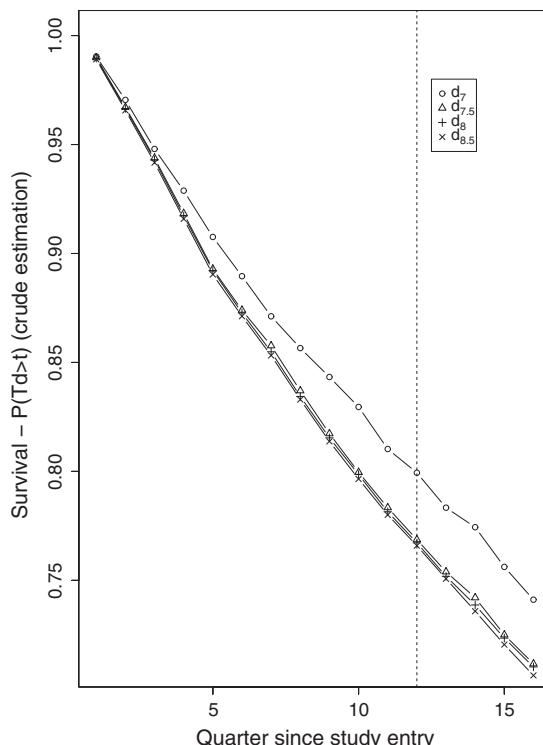


Figure 3. Crude estimates over 16 quarters of the four survival curves associated with the four treatment intensification initiation strategies d_θ with $\theta = 7, 7.5, 8, 8.5$.

Table II. Counts of the number of estimated stabilized inverse probability weights within specific intervals.

Weight range	g_n^θ	$g_{n,t}^\theta$	$g_{n,t,x}^\theta$	$g_{n,t,SL}^\theta$
<0	0	0	0	0
[0, 0.5[192,037	224,426	229,283	234,103
[0.5, 1[536,883	582,320	576,979	578,316
[1, 10[189,906	116,914	119,212	117,053
[10, 20[10,856	6581	4985	1482
[20, 30[986	610	410	2
[30, 40[187	62	40	0
[40, 50[62	19	19	0
[50, 100[38	7	24	0
[100, 150[1	4	3	0
≥ 150	0	13	1	0

For each the four approaches for estimating the weights, these counts describe the distribution of the weight estimates associated with all rule-person-time observations (930,956) consistent with a patient following any of the four treatment intensification decision rules d_θ with $\theta = 7, 7.5, 8, 8.5$. Note that if patients follow more than one rule at a given time point, their corresponding person-time observation is replicated as many times as the number of rules followed, and each replicate is assigned a separate stabilized inverse probability weight.

can then be viewed as an implicit way to restrict the proportion of large weights through smoothing with a misspecified model. This data analysis suggests that parametric estimation of the weights may instead lead to artificial violation of the positivity assumption in practice when the positivity assumption is in truth not violated. These remarks are supported by the examination of data (not shown) from individual patients who have estimated IP weights above 50 with g_n^θ while being below 50 with $g_{n,t,SL}^\theta$. Such data review shows that SL leads to better prediction of TI initiation and administrative end of study when patients actually initiate TI and remain uncensored. This improved prediction translates into smaller denominators for the IP weights and thus less variable IP weights, which then results in improving precision in the effect estimates with IPW estimation.

Whether extreme weighting is the result of true or artificial violation of the positivity assumption from misspecification of the model for g^θ , weight truncation [78–80] is often implemented in practice to improve the precision of IPW estimation. In this analysis, all IPW estimates were derived with and without truncation of the stabilized weights: all stabilized weights above 20 were replaced with value 20. The same rationale for truncating the IP weights applies to TMLE. Thus, following the same truncation scheme as the one implemented for IPW estimation, the unstabilized weights $1/\prod_{t=0}^k g_{A(t)}^\theta$ used in the ‘update steps’ of the TMLE algorithm were truncated at 20 divided by the corresponding numerator of the stabilized weights, that is, replaced by

$$\min \left(\frac{1}{\prod_{t=0}^k g_{A(t)}^\theta}, \frac{20}{\prod_{t=0}^k P(A(t) = d_\theta(\bar{L}(t)) | \bar{A}(t-1) = d_\theta(\bar{L}(t-1)))} \right)$$

As may be expected from the distributions of the untruncated stabilized weights resulting from the four approaches to estimate g^θ (Table II), weight truncation at 20 had very little impact on inferences in this study (results not shown). In particular, note that with SL, such weight truncation only concerns two rule-person-time observations for which the untruncated weight is below 30. Thus, weight truncation at 20 had essentially no impact on the IPW and TMLE results when the nuisance parameter g^θ is estimated with SL.

4. Targeted learning for efficiency gains

One motivation for the application of TMLE over IPW estimation is the potential for gain in estimation precision that may arise from the efficiency property of TMLE. Table I indicates however little increase in precision with TMLE because the ratios of the IPW SEs to the TMLE SEs range from 2% to 5% only

when g^θ is estimated with $g_{n,t,SL}^\theta$. As shown by equality (5) defining the influence curve of the TMLE estimator, gain in precision arises from minimization of the prediction errors from the estimate of the nuisance parameter Q^θ . Estimation precision is thus expected to be potentially improved with TMLE in problems where covariates can predict the outcome well. Lack of efficiency gains from the TMLE results in Table I could thus be the result of either the absence of good predictors of the outcome among the measured covariates or inadequate use of the measured covariates for estimating Q^θ (e.g., owing to model misspecification). Consistent estimation of the nuisance parameter Q^θ should thus result in improving estimation efficiency with TMLE. This motivates the application of SL for flexible estimation of Q^θ without relying on arbitrary learner choices such as the main-term logistic models considered by the DSA algorithm in the previous implementation of TMLE.

In addition, note that each element of the nuisance parameter Q^θ , that is, $Q_{L(k+1)}^\theta(\bar{L}(k))$ for $k = t_0, \dots, 0$, is potentially a function of the covariate history $\bar{L}(k)$ in the same way that each PS is potentially a function of past observed covariates. Because it is often assumed (possibly incorrectly) that the effect of early clinical measurements on current treatment decision is mediated by previous treatment decisions or the latest clinical measurements, the Markov assumption has often been made in practice, and only the last measurement of time-varying covariates are then considered as potential explanatory variables to estimate the PS for treatment initiation. So far, we largely relied on such Markov assumptions for estimating not only each PS but also the nuisance parameter Q . The only exception was for the A1c covariate because we considered not only the last measurement of A1c to estimate the five PS but also the last change in A1c measurements, that is, the difference between the last two A1c measurements. While Markov assumptions may be adequate for estimating the PS, it may be argued that clinical outcomes are the results of not only acute effects but also chronic effects, and Markov assumptions may thus not permit consistent estimation of the nuisance parameter Q^θ . In addition, some covariates in the observed data were assumed to be unrelated to treatment decisions and right censoring and were thus excluded from the list of explanatory variables to estimate g^θ . These covariates may however impact the outcome and should then be considered for consistent estimation of Q^θ .

For these reasons, we implemented TMLE of the RDs $\psi^{\theta_1, \theta_2}$ based on SL with an expanded list of explanatory variables for estimating the nuisance parameter Q^θ . More specifically, for each k , the list of candidate explanatory variables considered by SL to estimate $Q_{L(k+1)}^\theta(\bar{L}(k))$ was appended with the following:

- the indicators that A1c, Low-density lipoprotein (LDL), and ACR were measured in the current period;
- the indicator that the ACR is measured in the next period (i.e., that the patient is at risk of possible failure);
- the average of past A1c and LDL measurements;
- the average number of past imputed (with last value carried forward) A1c, LDL, and ACR measurements;
- the standard deviations of the past measurements of A1c and LDL;
- the numbers of past A1C measurements above 7, 7.5, 8, and 8.5;
- the numbers of past LDL measurements above 100, 130, 160, and 200;
- the baseline A1c, LDL, and ACR measurements;
- the difference between the baseline ACR measurement and the relevant ACR cutoff that would determine subsequent failure; and
- the difference between the last ACR measurement and the relevant ACR cutoff that would determine subsequent failure.

The following 57 candidate learners were considered to estimate $Q_{L(k+1)}^\theta(\bar{L}(k))$ separately with SL for each k and θ :

- one learner defined by the intercept logistic model;
- five learners defined by logistic models with only main terms for the most predictive explanatory variables identified by a significant p -value in univariate regressions with five significance levels ($\alpha = 0.3, 0.2, 0.1, 0.05, 1$);
- one learner defined by a logistic model with only main terms for 27 expert-selected covariates (all explanatory variables based on A1c, LDL, and ACR measurements);
- five learners defined by the stepAIC routine in R and based on five distinct sets of candidate explanatory variables identified by the following: (i) four significance levels ($\alpha = 0.3, 0.2, 0.1, 0.05$) and (ii) the same 27 expert-selected covariates;

- five neural network learners defined based on the same four significance levels and 27 expert-selected covariates;
- five learners defined by Bayes regression and based on the same four significance levels and 27 expert-selected covariates;
- five learners defined by polychotomous regression (`polyclass` with Bayesian information criterion) and based on the same four significance levels and 27 expert-selected covariates;
- five random forest learners based on the same four significance levels and 27 expert-selected covariates;
- five learners defined by bagging for classification trees and based on the same four significance levels and 27 expert-selected covariates; and
- 20 learners defined by generalized additive models with smoothing splines of degrees 2, 3, 4, or 5 and based on, for each of these degrees, the same four significance levels and 27 expert-selected covariates.

In addition to all main-term variables, all these learners also considered two-way interaction terms selected on each training set using the protocol described in Section 3.2 (see approach 3 for estimating g^θ).

Note that for all $k < t_0$, the outcome to be predicted when estimating $Q_{L(k+1)}^\theta(\bar{L}(k))$ is continuous between 0 and 1. Because the current R implementation of `polyclass` does not permit the prediction of continuous outcomes between 0 and 1, we modified the five learners based on polychotomous regression when $k < t_0$ by dichotomizing the outcomes in the fivefold training sets based on the 0.5 cutoff, that is, all outcomes above 0.5 were replaced by 1 and otherwise by 0. To greatly shorten the SL computing time, the same dichotomization was implemented as part of the random forest and bagging learners considered for $k < t_0$. In addition, for $k = t_0$, SL was only used to predict the outcome of patients who are at risk of failure, that is, for whom ACR was actually monitored. For all other patients, the estimate of $Q_{L(t_0+1)}^\theta(\bar{L}(t_0))$ was set to 0 by default.

Table III displays the results of TMLE based on the SL approach just described for estimating the nuisance parameter Q^θ (g^θ is estimated with $g_{n,t,SL}^\theta$). These results illustrate the potential for gains in efficiency with TMLE compared with IPW estimation because the IPW SEs are now 7–11% higher than those of the TMLE estimator.

5. Evaluation with a simulation study

Our claims about TMLE from the real-data analysis just presented are weakened by the lack of a true gold standard to which results may be compared. In addition, results from a single data set provide only anecdotal evidence to support general claims about the properties of an estimation approach. Thus, to rigorously demonstrate the consistency and efficiency property of TMLE, we now present results from a simulation study that evaluates the double robustness and gains in estimation precision that can potentially be achieved with TMLE in practice.

5.1. Simulation protocol

To simulate observed data O , we sequentially generated observations from the following data-generating distributions:

- (1) $L_1(0) \sim \mathcal{B}(0.05)$ where \mathcal{B} denotes the Bernoulli distribution (time-independent variable such as history of cardiovascular disease (CVD) at baseline).
- (2) If $L_1(0) = 1$, then $L_2(0) \sim \mathcal{B}(0.5)$, else $L_2(0) \sim \mathcal{B}(0.1)$ (baseline value of a time-dependent variable such as low vs. high A1c)
- (3) If $(L_1(0), L_2(0)) = (1, 0)$, then $A_1(0) \sim \mathcal{B}(0.5)$; else if $(L_1(0), L_2(0)) = (0, 0)$, then $A_1(0) \sim \mathcal{B}(0.1)$; else if $(L_1(0), L_2(0)) = (1, 1)$, then $A_1(0) \sim \mathcal{B}(0.9)$, else if $(L_1(0), L_2(0)) = (0, 1)$ then $A_1(0) \sim \mathcal{B}(0.5)$ (binary exposure such as an intensified treatment).
- (4) $A_2(0) \sim \mathcal{B}(0)$ (no censoring).
- (5) For $t = 1, \dots, 16$:
 - (a) $Y(t) \sim \mathcal{B}(1/(1+\exp(-(-6.5+L_1(0)+4L_2(t-1)+0.05*\sum_{j=0}^{t-1} I(L_2(j) = 0))))$ (indicator of failure such as onset or progression of albuminuria).

Table III. Comparison of inference from untruncated targeted minimum loss-based estimation (TMLE) and inverse probability weighting (IPW) estimation of the six risk differences at 3 years (12 quarters) based on super learning for estimating the nuisance parameters g^θ and Q^θ .

θ_1	θ_2	TMLE			IPW estimation			Relative efficiency $\frac{\sigma_n^{\theta_1,\theta_2}}{\sigma_n^{\theta_1,\theta_2,*}}$				
		$\psi_n^{\theta_1,\theta_2,*}$	$\psi_n^{\theta_1,\theta_2,*,+}$	p^*	$\sigma_n^{\theta_1,\theta_2,*}$	$\psi_n^{\theta_1,\theta_2}$	$\psi_n^{\theta_1,\theta_2,-}$					
8.5	8	7e-03	-4e-04	0.0143	0.064	3.8e-03	8e-03	1e-04	0.0159	0.046	4e-03	1.07
8.5	7.5	0.0221	9.3e-03	0.0349	1e-03	6.5e-03	0.0216	7.7e-03	0.0356	2e-03	7.1e-03	1.09
8.5	7	0.0386	0.0166	0.0606	1e-03	0.0112	0.041	0.0166	0.0655	1e-03	0.0125	1.11
8	7.5	0.0151	3.5e-03	0.0267	0.011	5.9e-03	0.0136	1e-03	0.0263	0.035	6.5e-03	1.09
8	7	0.0316	9.7e-03	0.0535	5e-03	0.0112	0.033	8.6e-03	0.0574	8e-03	0.0124	1.11
7.5	7	0.0165	-3.8e-03	0.0368	0.11	0.0103	0.0194	-3e-03	0.0418	9e-02	0.0114	1.11

Estimates based on TMLE versus IPW estimation are differentiated by the superscript * notation.

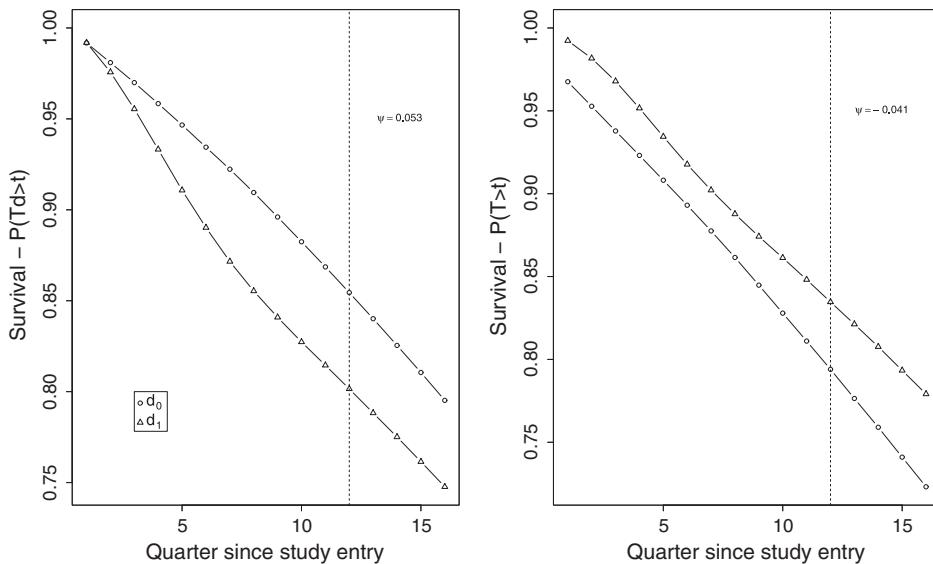


Figure 4. The plot on the left approximates the true counterfactual survival curves that define the causal effect of interest ψ . The plot on the right approximates the asymptotic limit of the crude estimator of the counterfactual survival curves with the observed data.

- (b) If $A_1(t-1) = 1$, then $L_2(t) \sim \mathcal{B}(0.1)$; else if $L_2(t) = 1$, then $L_2(t) \sim \mathcal{B}(0.9)$; else $L_2(t) \sim \mathcal{B}(\min(1, 0.1 + t/16))$.
- (c) If $A_1(t-1) = 1$, then $A_1(t) = 1$; else if $(L_1(0), L_2(t)) = (1, 0)$, then $A_1(t) \sim \mathcal{B}(0.3)$; else if $(L_1(0), L_2(t)) = (0, 0)$, then $A_1(t) \sim \mathcal{B}(0.1)$; else if $(L_1(0), L_2(t)) = (1, 1)$, then $A_1(t) \sim \mathcal{B}(0.7)$; else if $(L_1(0), L_2(t)) = (0, 1)$, then $A_1(t) \sim \mathcal{B}(0.5)$.
- (d) If $t = 16$, then $A_2(t) \sim \mathcal{B}(1)$ (administrative end of study); else $A_2(t) \sim \mathcal{B}(0)$ (no censoring).

Using the preceding protocol, we simulated 1000 observed data sets with $n = 50,000$ observations each. As described later, we implemented various TMLE and IPW estimators of the target parameter ψ defined as the difference between the cumulative risks of failure at $t_0 = 11$ (e.g., 3 years if t is measured in 90-day intervals) under two dynamic treatment strategies d_1 and d_0 : $\psi = P(Y_{d_1}(t_0 + 1) = 1) - P(Y_{d_0}(t_0 + 1) = 1)$. Each dynamic strategy d_θ was defined by the following rule: ‘Initiate treatment $A_1(t)$ the first time the covariate $L_2(t)$ is greater than or equal to θ and continue treatment thereafter’.

In addition, we approximated the true value of the targeted parameter ψ by repeating twice the simulation protocol just described where, each time, the exposure $A_1(t)$ was not generated randomly but assigned according to one of the two treatment strategies d_θ . Using this modified simulation protocol, we generated $n = 1,000,000$ observations of each counterfactual outcome $Y_{d_\theta}(t)$ for $\theta = 0, 1$ and $t = 1, \dots, 16$. The corresponding two survival curves are represented on the left plot of Figure 4, and we obtained $\psi \approx 0.053$.

To demonstrate that the observed data-generating distribution used in this simulation study leads to confounding bias, we also generated a separate large data set with $n = 1,000,000$ observations of O using the exact protocol described earlier (unmodified). Each person-time observation of the outcome $Y(t)$ in this data set was subsequently triaged in four mutually exclusive groups based on whether they followed a treatment regimen concordant with either strategy d_0 , d_1 , both, or neither. The survival curve associated with all person-time observations of the outcomes $Y(t)$ for $t = 1, \dots, 16$ concordant with strategy d_0 is represented on the right of Figure 4 along with its analog corresponding with d_1 . Comparisons of the survival curves on both plots of Figures 4 clearly demonstrate confounding bias because the unadjusted estimates of the survival curves (right plot) suggest a protective effect of late treatment initiation (d_1) while, in truth, late treatment initiation is simulated to be deleterious as shown by the counterfactual survival curves (left plot).

5.2. Illustration of double robustness

To illustrate the double-robust property of TMLE, we implemented both IPW estimation and TMLE using a correctly specified model for the action mechanism g^θ and two misspecified models denoted by

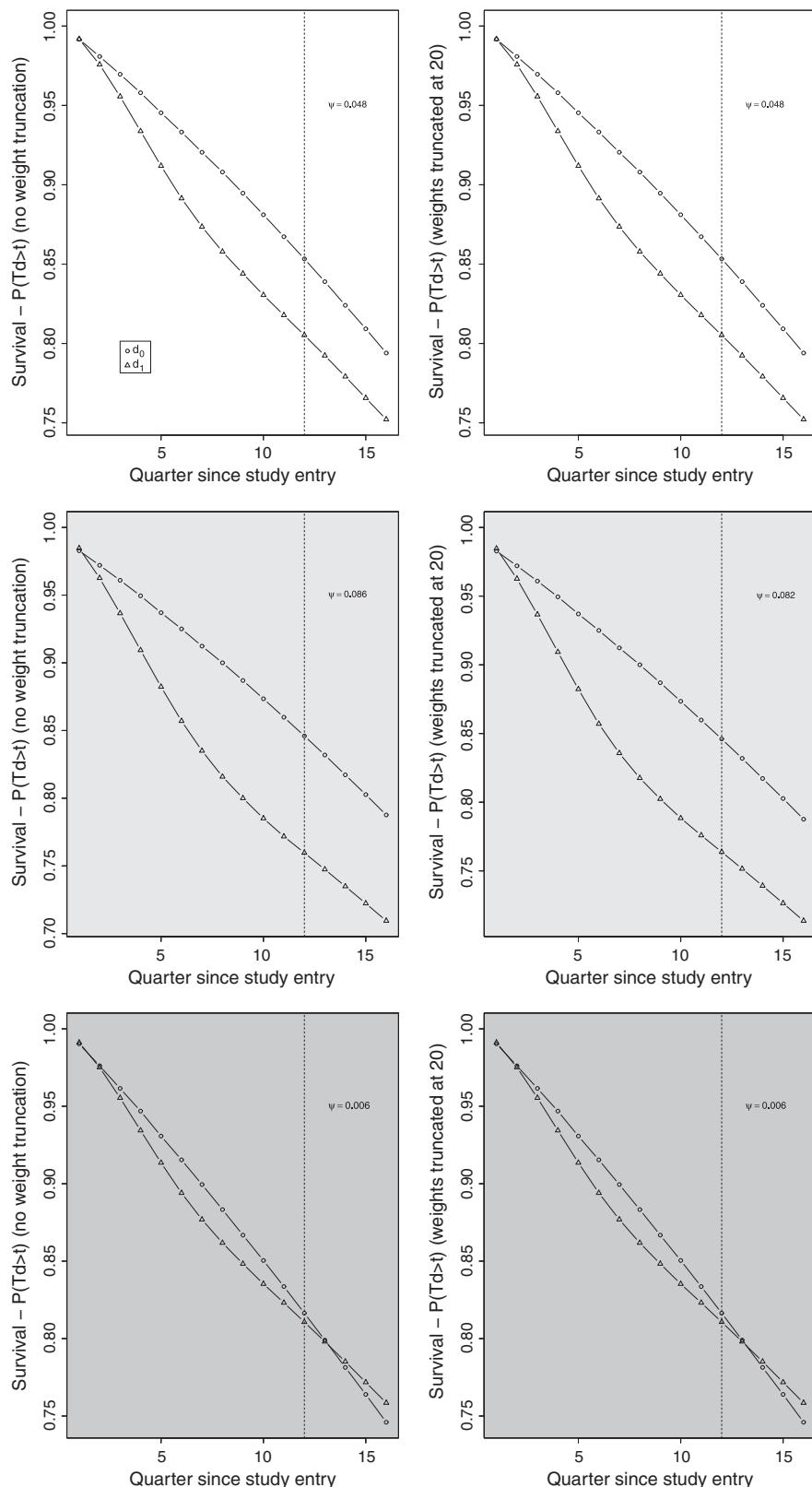


Figure 5. Each plot represents inverse probability weighting estimates of the two counterfactual survival curves corresponding with the two treatment strategies d_θ with $\theta = 0, 1$. The plots located in the top row are obtained based on the correctly specified models for the action mechanism g^θ . The plots located in the middle row are obtained based on a misspecified model for g^θ where a term for A1c is missing. The plots located in the bottom row are obtained based on a misspecified model for g^θ where a term for CVD is missing. The plots located in the right column are based on weight truncation at 20.

$g_{n,0}^\theta$, $g_{n,1}^\theta$, and $g_{n,2}^\theta$, respectively. More specifically, these three models of the action mechanism were respectively defined by

- Correct model: $\text{logit}(P(A_1(0) = 1 | L(0))) = \alpha_0 + \alpha_1 L_1(0) + \alpha_2 L_2(0)$, $\text{logit}(P(A_1(t) = 1 | \bar{L}(t), \bar{A}(t-2), A(t-1) = 0)) = \gamma_0 + \gamma_1 L_1(0) + \gamma_2 L_2(t)$, $P(A_1(t) = 1 | \bar{L}(t), \bar{A}(t-2), A(t-1) = 1) = 1$, $P(A_2(t) = 1) = 0$ for $t = 0, \dots, 15$, and $P(A_2(16) = 1) = 1$.
- Misspecified model missing a term for the time-dependent variable $L_2(t)$: $\text{logit}(P(A_1(0) = 1 | L(0))) = \alpha'_0 + \alpha'_1 L_1(0)$, $\text{logit}(P(A_1(t) = 1 | \bar{L}(t), \bar{A}(t-2), A(t-1) = 0)) = \gamma'_0 + \gamma'_1 L_1(0)$, $P(A_1(t) = 1 | \bar{L}(t), \bar{A}(t-2), A(t-1) = 1) = 1$, $P(A_2(t) = 1) = 0$ for $t = 0, \dots, 15$, and $P(A_2(16) = 1) = 1$.
- Misspecified model missing a term for the time-independent variable $L_1(t)$: $\text{logit}(P(A_1(0) = 1 | L(0))) = \alpha''_0 + \alpha''_2 L_2(0)$, $\text{logit}(P(A_1(t) = 1 | \bar{L}(t), \bar{A}(t-2), A(t-1) = 0)) = \gamma''_0 + \gamma''_2 L_2(t)$, $P(A_1(t) = 1 | \bar{L}(t), \bar{A}(t-2), A(t-1) = 1) = 1$, $P(A_2(t) = 1) = 0$ for $t = 0, \dots, 15$, and $P(A_2(16) = 1) = 1$.

TMLE was implemented based on the following model for Q^θ :

- $\text{logit}(E(Y(t_0 + 1) | \bar{A}(t_0) = d_\theta(\bar{L}(t_0)), \bar{L}(t_0), \bar{Y}(t_0) = 0)) = \mu_0 + \mu_1 L_1(0) + \mu_2 L_2(t_0) + \mu_3 \sum_{j=0}^{t_0} L_2(j)$.
- $\text{logit}(E(Q_{L(k+2)}^\theta(\bar{L}(k+1)) | \bar{A}(k) = d_\theta(\bar{L}(k)), \bar{L}(k), \bar{Y}(k) = 0)) = \rho_0 + \rho_1 L_1(0) + \rho_2 L_2(t_0) + \rho_3 \sum_{j=0}^k L_2(j)$ for $t = t_0 - 1, \dots, 0$.

To visually illustrate the consistency properties of the TMLE and IPW estimators (with and without truncation), we implemented them based on the preceding three models for g^θ using the simulated observed data set with $n = 1,000,000$ observations described earlier. Figure 5 represents the resulting six IPW estimates of the two counterfactual survival curves. Figure 6 represents the resulting six TMLE estimates of the two counterfactual survival curves. By comparison with the true counterfactual survival curves and their crude estimates represented in Figure 4, results in Figures 5 and 6 demonstrate the following: (1) successful adjustment for confounding bias with both the IPW and TMLE under correct specification of the model for the action mechanism; (2) inadequate adjustment for confounding bias with the two IPW estimators based on misspecified models for the action mechanism; and (3) successful adjustment for confounding bias with the TMLE estimators based on misspecified models for the action mechanism. The latter observation demonstrates the doubly robust property of TMLE.

To demonstrate that the preceding results are not due to cherry picking of a particular large simulated data set that favors TMLE over IPW estimation, we also report summaries of the IPW and TMLE estimates of the target parameter ψ over the 1000 simulated observed data sets with $n = 50,000$ observations each (described earlier). By comparison with the true value of the target parameter, the results in Table IV support the conclusions just described and indicates a minor gain in estimation efficiency with TMLE over IPW estimation of about 1.4%.

5.3. Illustration of efficiency gains

To illustrate the potential gains in efficiency with TMLE compared with IPW estimation, we modified the previous simulation protocol (referred to as protocol 1 from now on) to increase the predictive power of the covariates for the outcome while decreasing their predictive power for the exposure (to avoid near violation of the positivity assumption).

First, we modified simulation protocol 1 as follows and refer to the resulting protocol as protocol 2:

- Step 2 was changed to ‘If $L_1(0) = 1$ then $L_2(0) \sim \mathcal{B}(0.8)$, else $L_2(0) \sim \mathcal{B}(0.3)$ ’.
- Step 3 was changed to ‘If $(L_1(0), L_2(0)) = (1, 0)$ then $A_1(0) \sim \mathcal{B}(0.5)$, else if $(L_1(0), L_2(0)) = (0, 0)$ then $A_1(0) \sim \mathcal{B}(0.2)$, else if $(L_1(0), L_2(0)) = (1, 1)$ then $A_1(0) \sim \mathcal{B}(0.8)$, else if $(L_1(0), L_2(0)) = (0, 1)$ then $A_1(0) \sim \mathcal{B}(0.5)$ ’.
- Step 5a was changed to ‘ $Y(t) \sim \mathcal{B}(1/(1 + \exp(-(-7 + 2L_1(0) + 4L_2(t-1) + 0.03 * \sum_{j=0}^{t-1} I(L_2(j) = 0))))$ ’.
- Step 5c was changed to ‘If $A_1(t-1) = 1$ then $A_1(t) = 1$, else if $(L_1(0), L_2(t)) = (1, 0)$ then $A_1(t) \sim \mathcal{B}(0.4)$, else if $(L_1(0), L_2(t)) = (0, 0)$ then $A_1(t) \sim \mathcal{B}(0.2)$, else if $(L_1(0), L_2(t)) = (1, 1)$ then $A_1(t) \sim \mathcal{B}(0.8)$, else if $(L_1(0), L_2(t)) = (0, 1)$ then $A_1(t) \sim \mathcal{B}(0.6)$ ’.

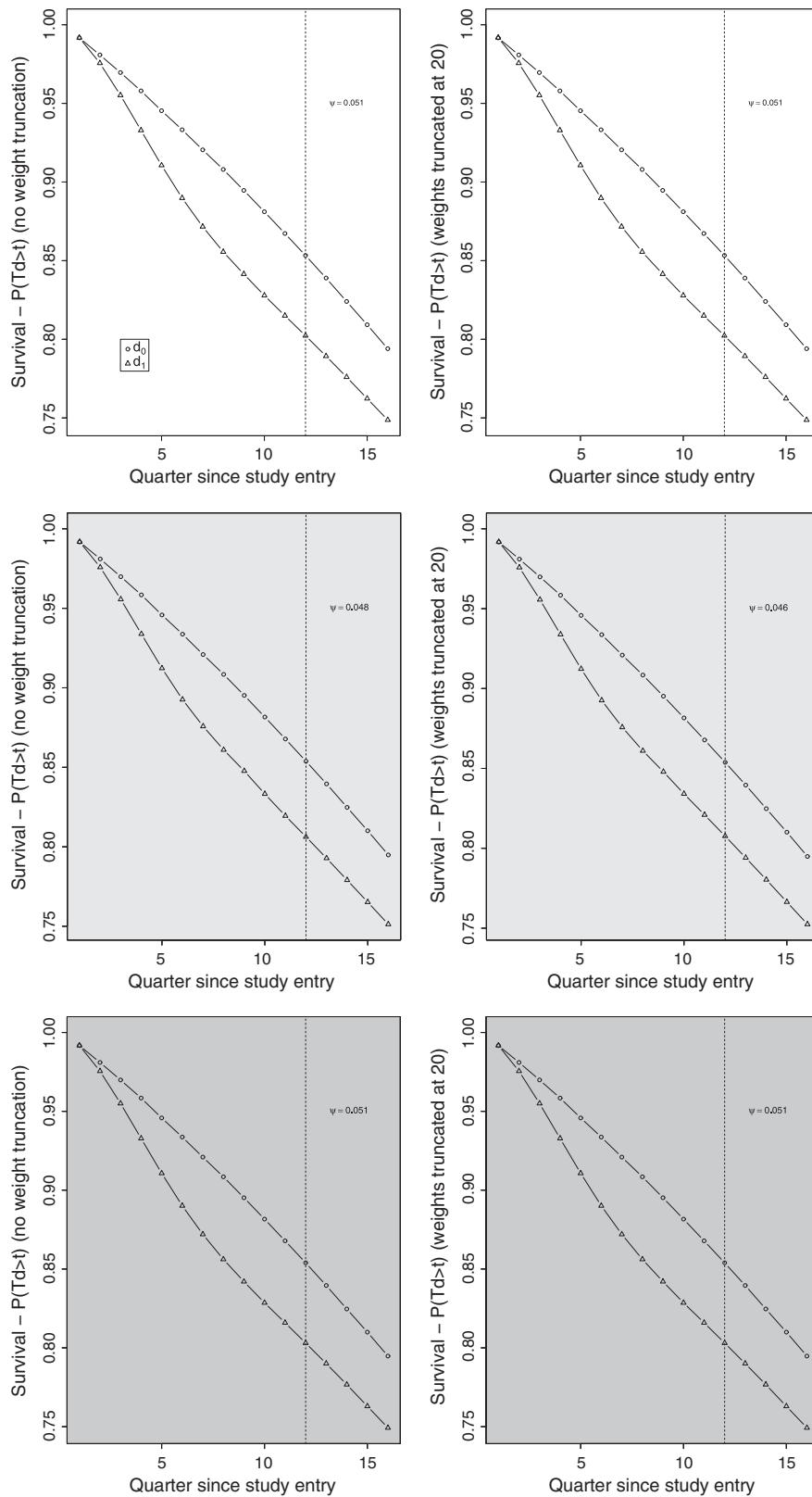


Figure 6. Each plot represents targeted minimum loss-based estimation estimates of the two counterfactual survival curves corresponding with the two treatment strategies d_θ with $\theta = 0, 1$. The plots located on the top row are obtained based on the correctly specified models for the action mechanism g^θ . The plots located on the middle row are obtained based on a misspecified model for g^θ where a term for A1c is missing. The plots located on the bottom row are obtained based on a misspecified model for g^θ where a term for CVD is missing. The plots located on the right column are based on weight truncation at 20.

Table IV. Comparison of inferences from untruncated and truncated targeted minimum loss-based estimation (TMLE) and inverse probability weighting (IPW) estimation of the cumulative risk difference at 3 years (12 quarters) based on the three approaches to estimate the nuisance parameter g^θ .

g_n^θ	Truncation	TMLE				IPW				Relative efficiency $\frac{\sigma_n}{\sigma_n^*}$
		ψ_n^*	Bias	σ_n^*	σ_{emp}^*	ψ_n	Bias	σ_n	σ_{emp}	
Correct model	✓	0.053	-7e-04	0.0054	0.0054	0.05	-0.0036	0.0055	0.0054	1.014
		0.053	-7e-04	0.0054	0.0054	0.05	-0.0036	0.0055	0.0054	1.014
Incorrect model 1 (no A1c term)	✓	0.049	-0.0047	0.0054	0.0059	0.088	0.0345	0.0063	0.0064	
		0.048	-0.0052	0.0054	0.0055	0.084	0.031	0.0058	0.0059	
Incorrect model 2 (no cardiovascular disease term)	✓	0.053	-4e-04	0.0054	0.0053	0.007	-0.0467	0.0053	0.0053	
		0.053	-4e-04	0.0054	0.0053	0.007	-0.0467	0.0053	0.0053	

Estimates based on TMLE versus IPW estimation are differentiated by the superscript * notation. The values for ψ_n^* and ψ_n are the average point estimates over 1000 simulated observed data sets. The values for σ_n^* and σ_n are the average estimates of the influence curve-based standard errors over 1000 simulated observed data sets. The values for σ_{emp}^* and σ_{emp} are the empirical standard deviation of the point estimates over 1000 simulated observed data sets.

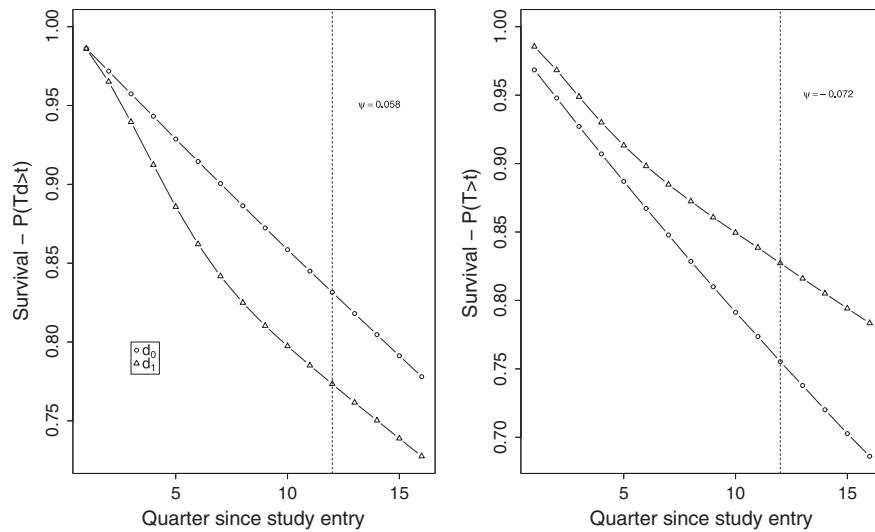


Figure 7. The plot on the left approximates the true counterfactual survival curves that define the causal effect of interest ψ when simulating data with protocol 2. The plot on the right approximates the asymptotic limit of the crude estimator of the counterfactual survival curves with the observed data.

Second, we modified simulation protocol 2 as follows and refer to the resulting protocol as protocol 3:

- Step 5a was changed to: ‘ $Y(t) \sim \mathcal{B}(1/(1 + \exp(-(-7 + 3L_1(0) + 5L_2(t-1) + 0.1 * \sum_{j=0}^{t-1} I(L_2(j) = 0))))$ ’.

The analogs of simulation results from protocol 1 in Figures 4–6 and Table IV are given in Figures 7–9 and Table V, respectively, when data are simulated using protocol 2 and in Figures 10–12 and Table VI, respectively, when data are simulated using protocol 3. These results again demonstrate both successful adjustment for confounding bias with TMLE and its double-robustness property. In addition, these results demonstrate increasing gains in estimation efficiency with increasing predictive power of the covariates for the outcome. When data are simulated with protocols 2 and 3, TMLE is about 11% and 38%, respectively, more efficient in estimating the cumulative RD at 3 years than IPW estimation (Tables V and VI).

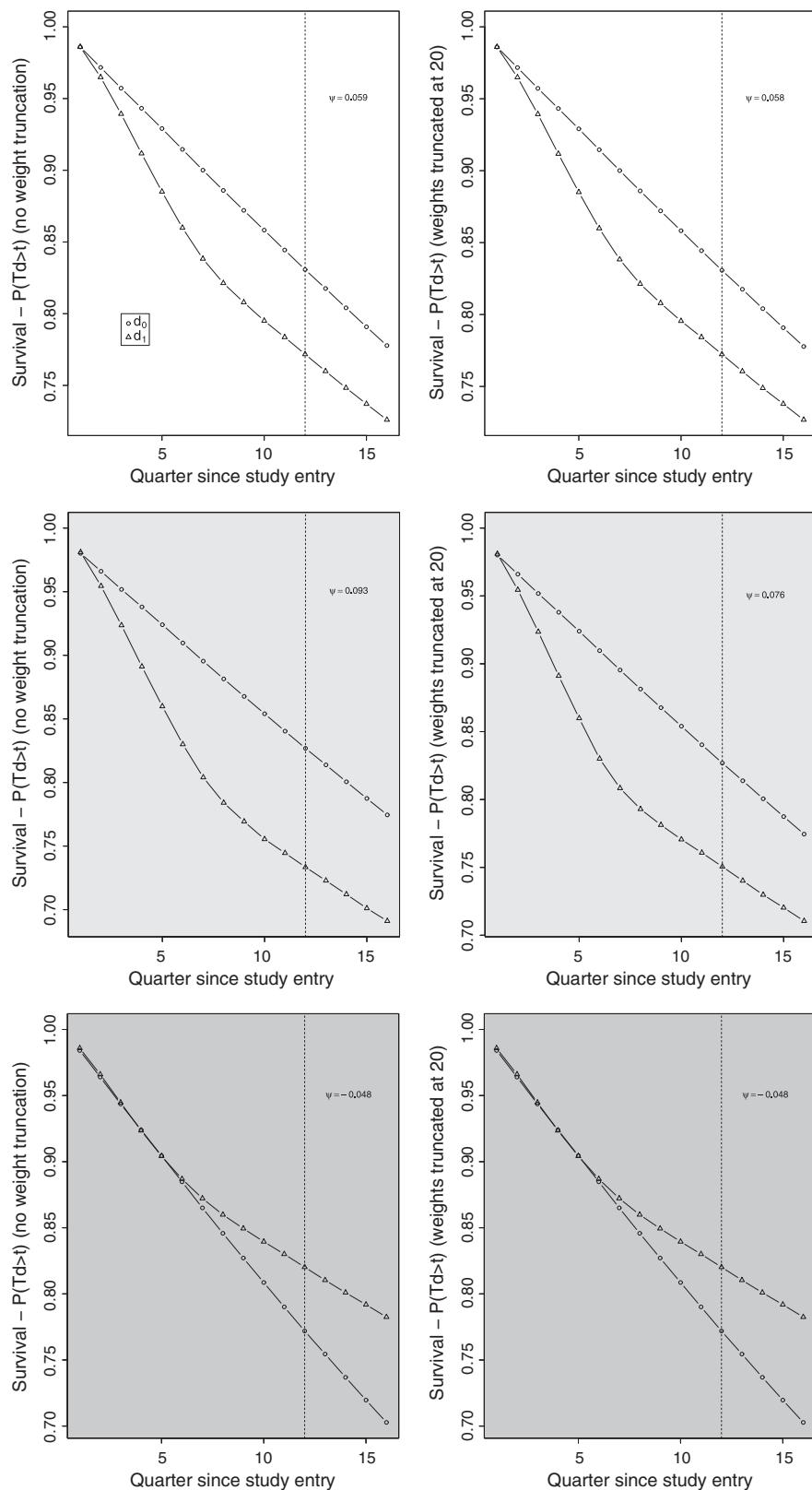


Figure 8. Each plot represents inverse probability weighting estimates of the two counterfactual survival curves corresponding with the two treatment strategies d_θ with $\theta = 0, 1$ when simulating data with protocol 2. The plots located in the top row are obtained based on the correctly specified models for the action mechanism g^θ . The plots located in the middle row are obtained based on a misspecified model for g^θ where a term for A1c is missing. The plots located in the bottom row are obtained based on a misspecified model for g^θ where a term for CVD is missing. The plots located in the right column are based on weight truncation at 20.

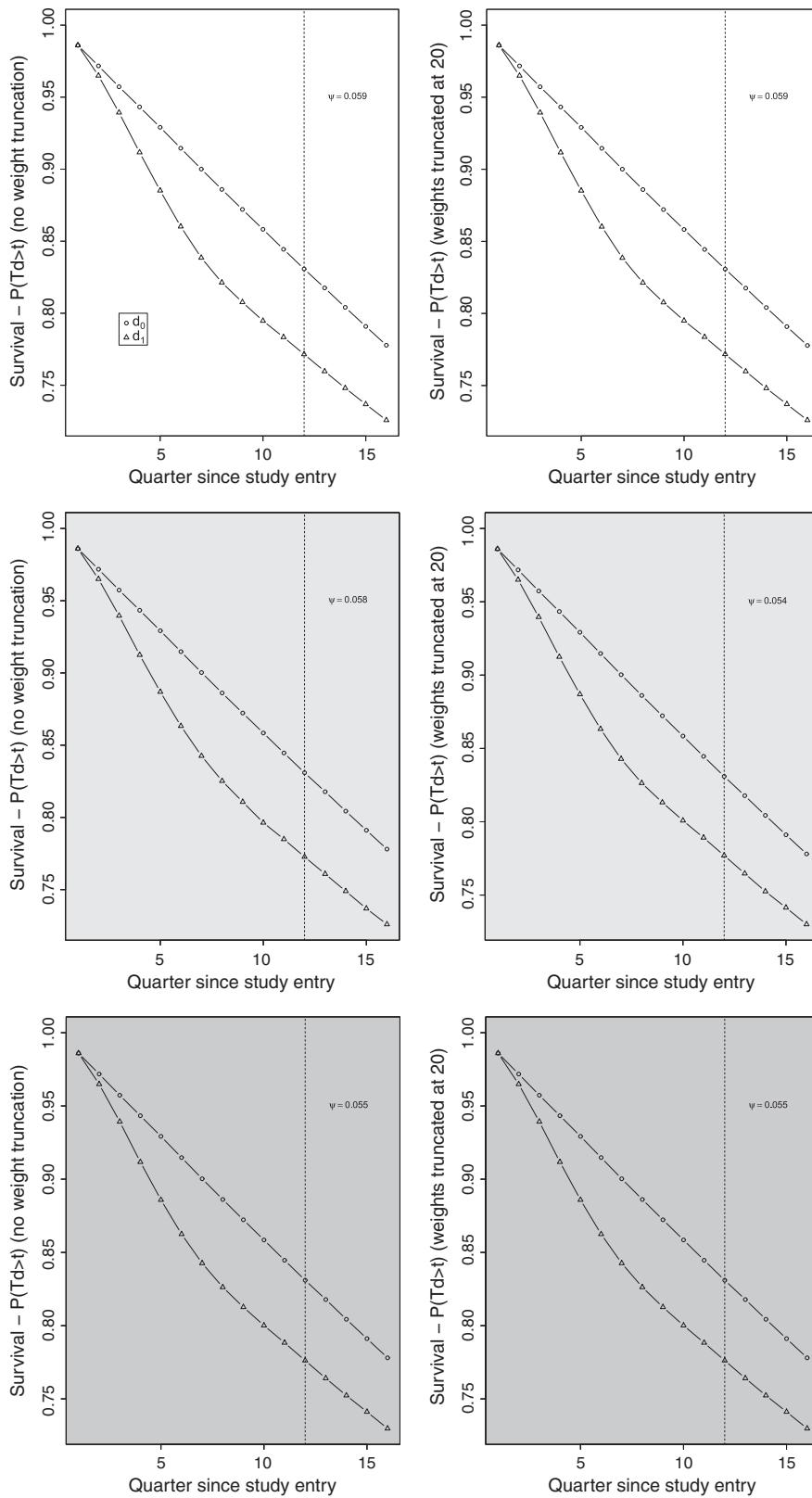


Figure 9. Each plot represents targeted minimum loss-based estimation estimates of the two counterfactual survival curves corresponding with the two treatment strategies d_θ with $\theta = 0, 1$ when simulating data with protocol 2. The plots located in the top row are obtained based on the correctly specified models for the action mechanism g^θ . The plots located in the middle row are obtained based on a misspecified model for g^θ where a term for A1c is missing. The plots located in the bottom row are obtained based on a misspecified model for g^θ where a term for CVD is missing. The plots located in the right column are based on weight truncation at 20.

Table V. Comparison of inferences from untruncated and truncated targeted minimum loss-based estimation (TMLE) and inverse probability weighting (IPW) estimation of the cumulative risk difference at 3 years (12 quarters) when data are simulated according to protocol 2 and based on the three approaches to estimate the nuisance parameter g^θ .

g_n^θ	Truncation	TMLE				IPW				Relative efficiency $\frac{\sigma_n}{\sigma_n^*}$
		ψ_n^*	Bias	σ_n^*	σ_{emp}^*	ψ_n	Bias	σ_n	σ_{emp}	
Correct model	✓	0.058 0.058	4e-04 -1e-04	0.006 0.0058	0.006 0.0057	0.058 0.058	3e-04 -5e-04	0.0067 0.0064	0.0063 0.006	1.11 1.111
Incorrect model 1 (no A1c term)	✓	0.058 0.054	-2e-04 -0.0043	0.006 0.0058	0.0092 0.0057	0.093 0.076	0.0347 0.0174	0.0101 0.0064	0.0101 0.0062	
Incorrect model 2 (no cardiovascular disease term)	✓	0.054 0.054	-0.0037 -0.0037	0.006 0.0058	0.0048 0.0048	-0.048 -0.048	-0.1065 -0.1065	0.0048 0.0048	0.0048 0.0048	

Estimates based on TMLE versus IPW estimation are differentiated by the superscript * notation. The values for ψ_n^* and ψ_n are the average point estimates over 1000 simulated observed data sets. The values for σ_n^* and σ_n are the average estimates of the influence curve-based standard errors over 2000 simulated observed data sets. The values for σ_{emp}^* and σ_{emp} are the empirical standard deviation of the point estimates over 1000 simulated observed data sets.

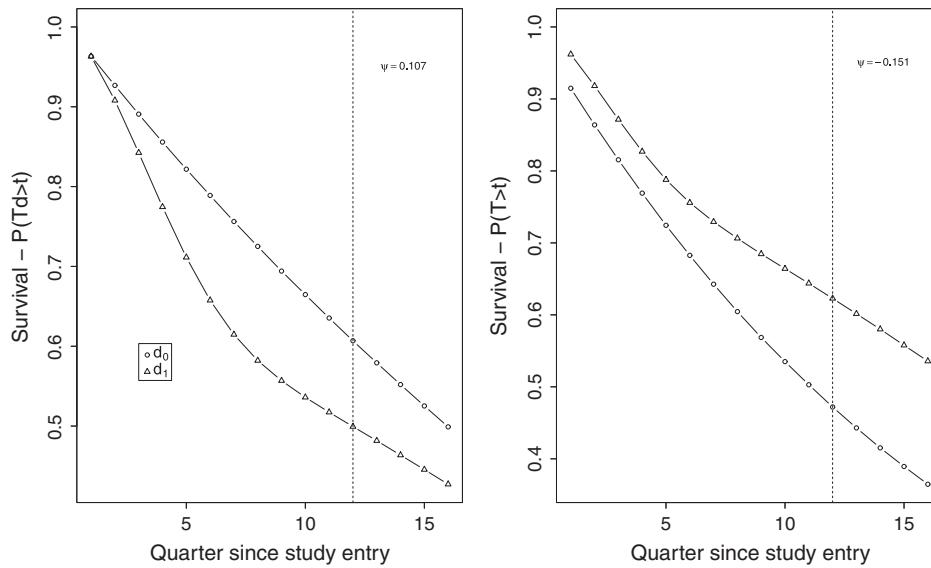


Figure 10. The plot on the left approximates the true counterfactual survival curves that define the causal effect of interest ψ when simulating data with protocol 3. The plot on the right approximates the asymptotic limit of the crude estimator of the counterfactual survival curves with the observed data.

6. Discussion

Our interpretation of the main results from the analysis of the real-world CER study (i.e., successful adjustment for time-dependent confounding and selection bias and efficiency gain with TMLE) is largely supported by previous results from the complementary simulation study. Tables VII and VIII summarize and compare various aspects of the IPW estimation and TMLE algorithms considered in this report. In particular, the real-data analysis suggests that bias in the estimation of the action mechanism g^θ may differentially impact point and interval estimation with TMLE and IPW estimation. In this one study, while point estimation with both methods and interval estimation with IPW estimation were relatively robust to minor bias in estimation of the action mechanism g^θ , interval TMLE based on the estimator's influence curve was sensitive to such bias. This observation suggests the use of bootstrapping to evaluate the bias of estimators of the action mechanism and guide the selection of the estimator based on which TMLE inference should be derived in practice; for example, the data-adaptiveness of the estimation approach

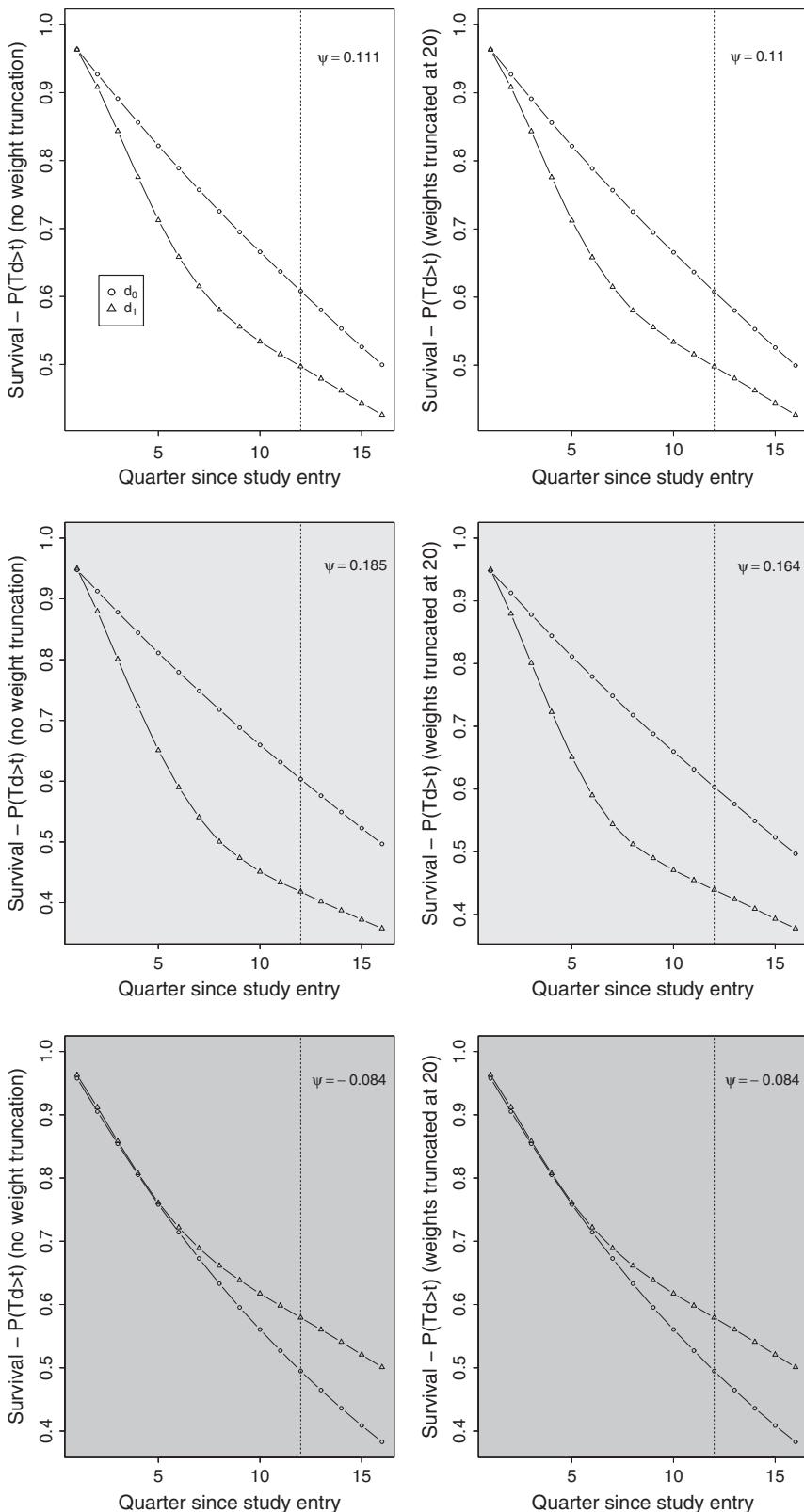


Figure 11. Each plot represents inverse probability weighting estimates of the two counterfactual survival curves corresponding with the two treatment strategies d_θ with $\theta = 0, 1$ when simulating data with protocol 3. The plots located in the top row are obtained based on the correctly specified models for the action mechanism g^θ . The plots located in the middle row are obtained based on a misspecified model for g^θ where a term for A1c is missing. The plots located in the bottom row are obtained based on a misspecified model for g^θ where a term for CVD is missing. The plots located in the right column are based on weight truncation at 20.

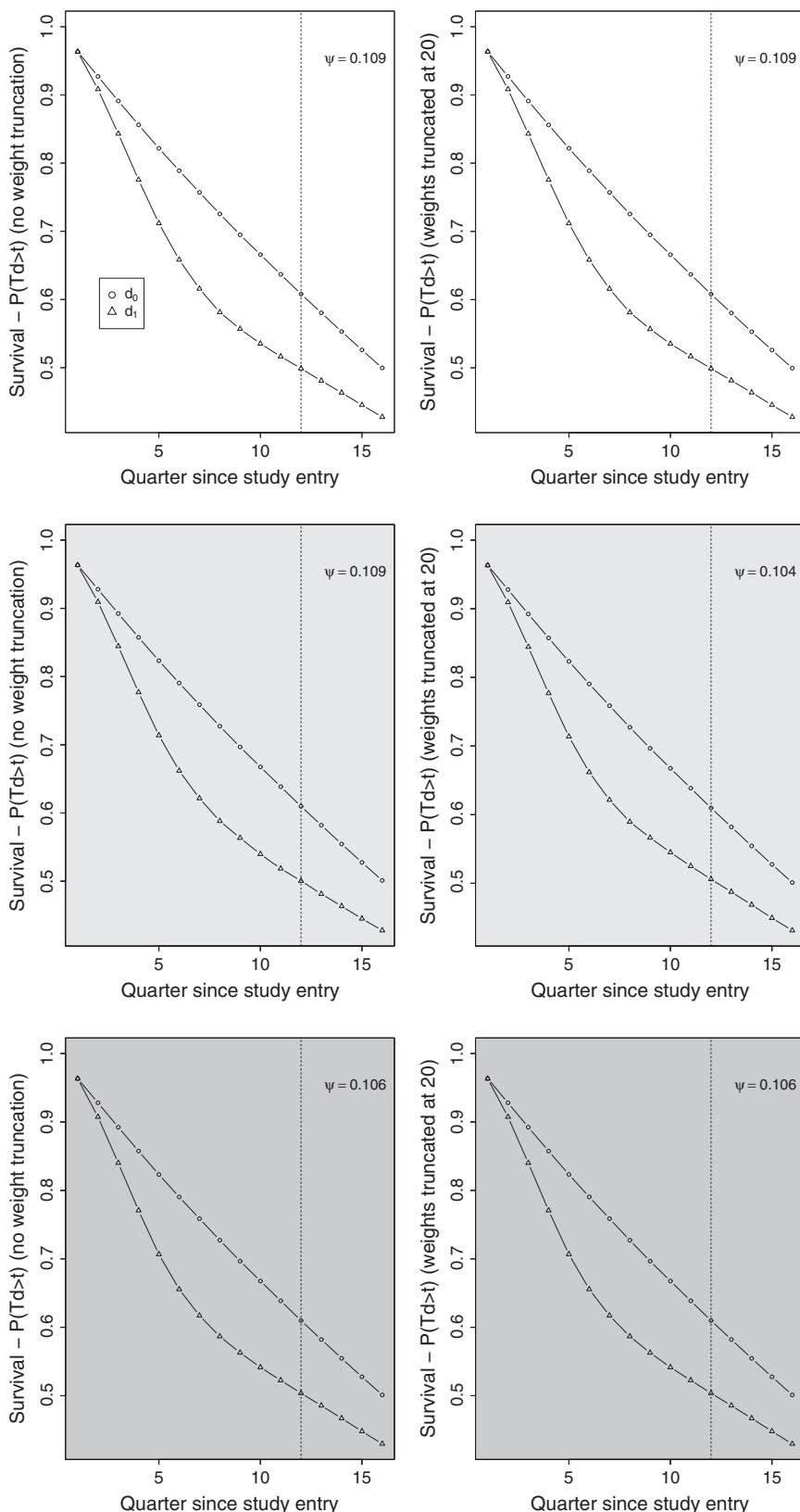


Figure 12. Each plot represents targeted minimum loss-based estimation estimates of the two counterfactual survival curves corresponding with the two treatment strategies d_θ with $\theta = 0, 1$ when simulating data with protocol 3. The plots located in the top row are obtained based on the correctly specified models for the action mechanism g^θ . The plots located in the middle row are obtained based on a misspecified model for g^θ where a term for A1c is missing. The plots located in the bottom row are obtained based on a misspecified model for g^θ where a term for CVD is missing. The plots located in the right column are based on weight truncation at 20.

Table VI. Comparison of inferences from untruncated and truncated targeted minimum loss-based estimation (TMLE) and inverse probability weighting (IPW) estimation of the cumulative risk difference at 3 years (12 quarters) when data are simulated according to protocol 3 based on the three approaches to estimate the nuisance parameter g^θ .

g_n^θ	Truncation	TMLE				IPW				Relative efficiency $\frac{\sigma_n}{\sigma_n^*}$
		ψ_n^*	Bias	σ_n^*	σ_{emp}^*	ψ_n	Bias	σ_n	σ_{emp}	
Correct model	✓	0.108	0.001	0.0059	0.006	0.108	0.0011	0.0082	0.0078	1.392
		0.107	6e-04	0.0058	0.0058	0.107	2e-04	0.008	0.0075	1.376
Incorrect model 1 (no A1c term)	✓	0.109	0.0019	0.0059	0.0074	0.182	0.075	0.0106	0.0107	
		0.103	-0.0041	0.0058	0.0063	0.162	0.0557	0.0078	0.0076	
Incorrect model 2 (no cardiovascular disease term)	✓	0.105	-0.0019	0.006	0.0056	-0.085	-0.1917	0.0063	0.0066	
		0.105	-0.0019	0.0058	0.0056	-0.085	-0.1917	0.0063	0.0066	

Estimates based on TMLE versus IPW estimation are differentiated by the superscript * notation. The values for ψ_n^* and ψ_n are the average point estimates over 1000 simulated observed data sets. The values for σ_n^* and σ_n are the average estimates of the influence curve-based standard errors over 1000 simulated observed data sets. The values for σ_{emp}^* and σ_{emp} are the empirical standard deviation of the point estimates over 1000 simulated observed data sets.

Table VII. Comparison of the properties of inverse probability weighting (IPW) estimation and targeted minimum loss-based estimation (TMLE).

	TMLE	IPW
Applicable to effects represented by a nonparametric/saturated MSM	✓	✓
Applicable to effects represented by a non-saturated MSM	An alternate algorithm was recently proposed [81]	✓ (e.g., [46])
Assumptions required for effect identifiability		
No unmeasured confounders	✓	✓
Positivity	✓	✓
Proper adjustment for time-dependent confounding and selection bias	+ Doubly robust	- Not doubly robust
Proper analytic variance estimation	- Sensitive to bias in g^θ estimation	+ Robust to bias in g^θ estimation
Precision	+	-
Feasibility with large, high-dimensional data	+	+
Programming burden		
Point estimation	-	+
Analytic variance estimation	+	+
Computing time	-	+

The + and - signs indicate relative (potential) advantages/limitations.

for g^θ may be sequentially increased until there is a match between the two estimates of TMLE variance obtained analytically based on the estimator's influence curve and based on bootstrapping.

Super learning was shown here to be a viable practical data-adaptive estimation approach for the action mechanism despite the common intuition that data-adaptive estimation may not be desirable in practice for fear of revealing violations of the positivity assumption. Instead, estimation based on parametric models—even if misspecified—may then be preferred in practice because it is viewed as an implicit way to restrict the proportion of large IP weights through smoothing. The results in this report suggest however that the estimation approaches for the action mechanism that are commonly used in practice based on arbitrary parametric models may lead to artificial violation of the positivity assumption (extreme IP weights) when this assumption is in truth not violated.

Table VIII. Comparison of the properties of the various estimators of $\psi^{\theta_1, \theta_2}$ implemented in this report.

	g_n^θ		$g_{n,t}^\theta$		$g_{n,t,\times}^\theta$		$g_{n,t,SL}^\theta$		
	IPW	TMLE $Q_{n,DSA}^\theta$	IPW	TMLE $Q_{n,DSA}^\theta$	IPW	TMLE $Q_{n,DSA}^\theta$	IPW	TMLE $Q_{n,DSA}^\theta$	TMLE $Q_{n,SL}^\theta$
'Sufficient'* adjustment for time-dependent confounding and selection bias	✓	✓	✓	✓	✓	✓	✓	✓	✓
Proper† analytic estimation of variance (or ranking by increasing discrepancy with bootstrap estimation)	✓	9	✓	8	✓	7	✓	✓	✓ (not checked‡)
Precision (ranking by increasing variance estimated by bootstrapping or analytically if valid)	9	8§	6.5	4.5§	6.5	4.5§	3	2	1
Robustness to arbitrary parametric assumptions (ranking by decreasing robustness)	9	8	7	6	5	4	3	2	1
Computing burden (ranking by increasing burden)	1	2	3	4	5	6	7	8	9

The two estimators of the nuisance parameter Q^θ based on the DSA algorithm and SL are denoted by $Q_{n,DSA}^\theta$ and $Q_{n,SL}^\theta$, respectively.

*By 'sufficient', we mean that the inference is concordant with the results from previous randomized trials; that is, the six cumulative risk difference estimates indicate a clear differentiation and consistent ordering of the effectiveness of the four dynamic treatment interventions to support an increasing beneficial effect of more aggressive therapy initiation rules.

†Determined by concordance with bootstrap estimation.

‡Theoretically inferred based on the concordance between the analytic and bootstrap estimates of the variance of TMLE based on $g_{n,t,SL}^\theta$ and $Q_{n,DSA}^\theta$, which suggests consistent estimation of g^θ with $g_{n,t,SL}^\theta$.

§Estimated by bootstrapping (data not shown).

The implementation of TMLE in this work also underscored the need for estimation of all components of the action mechanism even if one or more components are assumed to be uninformative, for example, conditional probabilities of censoring by administrative end of study. Unlike weight stabilization in IPW estimation, which allows the analyst to ignore estimation of 'uninformative components' of the action mechanism because weight stabilization results in cancellation of the corresponding conditional probabilities in the denominator and numerator of the weights, weight stabilization is not possible with the proposed TMLE algorithm and estimates of all components of the action mechanism are thus always needed in practice.

While IPW estimation is grounded in a formal theoretical framework that is opaque to many applied researchers, its implementation is simple enough that some intuitive explanations are available to provide insights into its ability to adjust for confounding and selection bias in practice (e.g., weighting of the observed data results in ghost/pseudo-data where confounders are no longer associated with exposures as if patients had actually been randomized to the exposure of interest) [82]. While the targeted learning algorithm evaluated in this report is also grounded in theory, there is however no intuitive explanations for justifying its ability to adjust for confounding and selection bias. This report demonstrates that a seemingly convoluted algorithm with no intuitive support is not only computationally feasible (see R code in Appendices 6 and 6) in real-world CER based on large healthcare databases but also, most importantly, on par with IPW estimation in performance with confounding and selection bias adjustment in CER that involve time-varying confounders on causal pathways between the time-varying exposures and outcome. In addition, this report illustrates the algorithm's potential for improving inferences through gains in estimation efficiency compared with IPW estimation.

In practice, however, such gains in efficiency may only reflect overfitting in the estimation of the nuisance parameter Q^θ (formula (5)). Estimation methods based on cross-validation for the selection of estimators of the nuisance parameters (such as the DSA algorithm or SL) can then provide protection against such incorrect inferences with TMLE. Unlike estimation of the action mechanism g^θ for which assumptions like the Markov assumption may often be realistically invoked to simplify estimation by

only considering the most recent treatment and covariate histories as explanatory variables (e.g., for predicting treatment initiation), results in this report suggest that estimation of Q^θ should generally rely on a richer set of both treatment and covariate histories to realize efficiency gains with TMLE because simplifying assumptions that may apply to components of the action mechanism are not expected to extend to the nuisance parameter Q^θ in general. If these simplifying assumptions are nevertheless made, suboptimal efficiency gains are expected with TMLE owing to inconsistent estimation of Q^θ .

In addition, while the IPW estimation approach insures that the estimated survival curves are monotone decreasing, the TMLE estimator does not. Isotonization of the estimated survival curves derived by TMLE can be used in practice to enforce monotonic decrease of the estimates of survival probabilities over time. Inference can then be derived based on recent results that have shown that the influence curve of the isotonized estimator of a counterfactual survival curve is identical to the influence curve of the original estimator [83]. Isotonization was not needed here because all estimated survival curves were monotone decreasing.

Furthermore, the nonparametric MSM approach adopted in this report may not always be realistic in practice as very little data may be available to contrast the interventions of interest with precision (curse of dimensionality). In such cases, one may revert back to the convenient but elusive approach that consists in arbitrarily choosing a non-saturated MSM, which is expected to be misspecified and thus likely inadequate to provide a consistent estimate of the parameter of interest. Instead, a nonparametric MSM approach based on a *working, non-saturated model* [84] can be adopted to explicitly recognize the limitation of an arbitrarily specified non-saturated MSM in capturing the true parameter of interest $\psi^{\theta_1, \theta_2}$. The approach consists in replacing the parameter $\psi^{\theta_1, \theta_2}$ with a new parameter of interest defined by minimizing the distance between the true survival curves of interest and their estimates from a working model (referred to as a working MSM). Informally, such a nonparametric MSM approach aims to emulate inference from an ideal randomized trial (perfect compliance and no loss to follow-up) that is based on a working (likely misspecified) model for the survival curves in each treatment arm. Similar to IPW estimation, which can be adapted to estimate the parameters defined by such an MSM approach [84], the TMLE algorithm studied in this report can be modified to accommodate such an approach as recently described in a technical report [81] and implemented in an R package [85].

Although this work focused on the application of TMLE in CER with observational data, TMLE like IPW estimation is also relevant in randomized experiments with non-adherence and loss to follow-up to properly account for time-dependent confounding and selection bias in ‘as treated’ or ‘per protocol’ analyses [86] or to increase estimation efficiency without jeopardizing consistency in intention-to-treat analyses that incorporate covariate information collected prior to randomization [87]. The theoretical properties of the targeted learning approach have thus the potential to greatly impact CER through improved confounding and selection bias adjustment (double robustness and data-adaptive estimation) but also more precise effect estimates (efficiency property). Concretely, targeted learning could lead to more reliable effect estimates, earlier detection of effectiveness or safety signals, or the ability to detect differential subgroup effects with smaller sample sizes. While these potential advantages are theoretically derived from the large-sample (asymptotic) properties of TMLE, concerns over possible undesirable finite-sample properties that cannot be predicted from theory may be raised. The results in this report do not substantiate such concerns and also do the following: (1) demonstrate the feasibility of TMLE in real-world CER; (2) illustrate the ability of TMLE to properly account for time-dependent confounding and selection bias; and (3) elicit practical evidence of the potential for efficiency gains with TMLE over IPW estimation. While these results motivate further applied investigation of TMLE, they are not meant as a compelling argument for the routine application of TMLE instead of IPW estimation. In this one study, only a relatively modest gain in estimation precision was demonstrated with real-world data at the cost of an increased computing burden with SL. Additional research is needed to continue evaluation of the translation of TMLE’s theoretical properties into practice (finite-sample properties) and, in particular, to evaluate the algorithm’s double-robustness property and to develop a computationally feasible algorithm to estimate TMLE variability when one does not want to rely solely on consistent estimation of the action mechanism (i.e., consistent estimation of the nuisance parameter g^θ).

Appendix A. R code for targeted minimum loss-based estimation implementation

The following R code was used to implement TMLE point estimation and to derive inference based on the estimator’s influence curve. It references the following R objects in the working directory:

- `Odata` is a data frame containing the observed data O . Each row contains the observation of the covariates $L_i(t)$ and the action $A_i(t)$ for a given time point t and a given patient i . The columns `Study_ID` and `period` of `Odata` contain the patient identifiers i and time points t , respectively. The columns `TI` and `C` contain the observations of $A_1(t)$ and $A_2(t)$, respectively. The columns `T.tilde` and `DELTA` contain the follow-up times \tilde{T} and indicators of failure Δ , respectively. The column `unstabIPAW` contains (previously derived) estimates of the unstabilized IP weights. Columns of `Odata` also include the four indicators (named `d7`, `d7.5`, `d8`, and `d8.5`) that the covariate observation $L_i(t)$ is measured after exposure according to a treatment history $\bar{A}_i(t-1)$ concordant with one of the four dynamic rules of interest (d_7 , $d_{7.5}$, d_8 , and $d_{8.5}$, respectively). The columns `numd7`, `numd7.5`, `numd8`, and `numd8.5` contain the (previously derived) estimates of the stabilization factors for the IP weights associated with observations $L_i(t)$ measured after exposure according to a treatment history concordant with the dynamic rules d_7 , $d_{7.5}$, d_8 , and $d_{8.5}$, respectively. All columns in `Odata` with a name in the R object `Ls.DSA` (see description later) must contain numeric values (no factor/character values). Rows must be ordered by patient identifier and time (i.e., increasing values in, first, the `Study_ID` column and, second, the `period` column).
- `Ls` is a vector of character strings that are the names of a subset of the columns of `Odata` that contain the observations of the covariates $L_i(t)$.
- `Ls.DSA` is a vector with the names of all covariates $L(t)$ that are considered as candidate explanatory variables by the machine algorithm ‘DSA’ for the purpose of estimating the nuisance parameters Q^θ . All variable names in `Ls.DSA` must also be column names of `Odata`.
- `Yname` is the name of the column of `Odata` that contains the observations of $Y_i(t)$.

A. 1. Point estimation

```
### load the DSA package available at 'http://www.stat.berkeley.edu/~laan/Software/' :
library(DSA)

#####
##### ROUTINE FOR TMLE POINT ESTIMATION #####
#####

### Arguments to provide to the routine:
### 't0' is the time point when the cumulative risk of interest is estimated
### 'theta' identifies the dynamic intervention of interest (7, 7.5, 8, or 8.5)
### 'Q.L.t.DSA' is a list of (previously derived) DSA estimators of the elements of the nuisance
### parameter Q^theta (optional).
### 'truncate.level' defines, when strictly positive, the truncation level for estimates of the IP
### weights. Estimates of the IP weights are left untruncated when a negative value is provided.
### 'browse=TRUE' is used for debugging purposes.

get.TMLE.pt.est <- function(t0, theta, Q.L.t.DSA=NULL, truncate.level=-1, browse=FALSE){

  if(browse) browser()

  dtheta <- paste("d", theta, sep="")
  t <- t0 # algorithm starts with estimation of Q(bar{L}(t))=E( Q(bar{L}(t+1)) | bar{A}(t)=dtheta, bar{
    L}(t), bar{Y}(t)=0 ) for t=t0
  Q.L.t.DSA.out <- Q.L.t.update.out <- Q.L.t.tmle.n.extended <- vector("list", t0+1)
  if(is.null(Q.L.t.DSA)){ # initial estimators of Q^theta will be estimated with the DSA algorithm
    Q.L.t.DSA <- vector("list", t0+1)
    Q.data.adaptive <- TRUE
  } else{ # initial estimators of Q^theta are provided by the user
    Q.data.adaptive <- FALSE
  }

  while(t>=0){

    cat("\n Q(L(,t,))\n", sep="")
    ## Prepare the data needed for initial estimation of Q(bar{L}(t)) (steps 2 and 4.a in Section 3.1)
    ## Extract the subset of person-time observations relevant for estimation of Q(bar{L}(t))
    subsetQ <- which(Odata[, "period"]%in%t & Odata[, Yname]%in%0 & Odata[, dtheta]%in%1)

    ## Extract the independent variables and IP weights to estimate Q(bar{L}(t))
    QX.L.t.data <- Odata[ subsetQ ,c("Study_ID", "period", "TI", "C", "dtheta", "unstabIPAW", paste("numd",
      theta, sep=""))]
  }
}
```

```

## Extract the subset of person-time observations relevant for estimation of Q(bar{L})(t)
subsetQ <- which(Odata[, "period"]%in%t & Odata[, Yname]%in%0 & Odata[, dtheta]%in%1)

## Extract the independent variables and IP weights to estimate Q(bar{L})(t)
QX.L.t.data <- Odata[ subsetQ ,c("Study_ID","period","TI",Ls,"C",dtheta,"unstabIPAW",paste("numd",
    theta ,sep=""))]

## Extract the dependent variable to estimate Q(bar{L})(t)
if(t==t0){ # collect outcome data for regression in step 2 of Section 3.1
    QY.L.t.data <- Odata[ subsetQ+1 , c("Study_ID","period",Yname)]
    QY.L.t.data.tmp <- QY.L.t.data[,Yname]
    names(QY.L.t.data.tmp) <- QY.L.t.data[, "Study_ID"]
    QY.L.t.data <- QY.L.t.data.tmp
} else{ # collect outcome data for regression in step 4.a of Section 3.1
    QY.L.t.data <- rep(NA,nrow(QX.L.t.data))
    names(QY.L.t.data) <- QX.L.t.data[, "Study_ID"]
    ## group 1: patients who followed rule up to t+1
    QY.L.t.data[ names(Q.L.t.tmle.n) ] <- Q.L.t.tmle.n
    ## group 2: patients who followed rule up to t only but not t+1 (extrapolation)
    idgroup2 <- names(QY.L.t.data)[is.na(QY.L.t.data)]
    ## 2 subgroups in group 2:
    ## subgroup 1 - patients with Y=1 before t while on dtheta
    QY.L.t.data[idgroup2%in%names(Q.L.t.tmle.n.1)] <- 1
    ## subgroup 2 - the others (note that 't+1'='previous t in the while loop')
    data.extrap <- Odata[ Odata[, "Study_ID"]%in%idgroup2[!idgroup2%in%names(Q.L.t.tmle.n.1)] & Odata
        [, "period"]%in%(t+1) ,]
    Q.L.t.n.offset.group2 <- predict(Q.L.t.glm,newdata=data.extrap)
    Q.L.t.tmle.n.group2 <- 1/(1+exp(-(Q.L.t.n.offset.group2+Q.L.t.tmle$coef)))
    names(Q.L.t.tmle.n.group2) <- data.extrap[, "Study_ID"]
    QY.L.t.data[ names(Q.L.t.tmle.n.group2) ] <- Q.L.t.tmle.n.group2
    Q.L.t.tmle.n.extended[[t0-t]] <- c(Q.L.t.tmle.n.extended[[t0-t]],Q.L.t.tmle.n.group2)
}

Q.L.t.data <- cbind(QX.L.t.data , "Q.n"=QY.L.t.data) # data ready for initial regression to estimate
Q

if(Q.data.adaptive){
    ## Select model for Q(bar{L})(t)) with DSA algorithm to define the initial estimator described in
    ## steps 2 and 4.a of Section 3.1
    Q.DSA <- DSA(Q.n ~ 1, data = Q.L.t.data[,c(Ls.DSA,"Q.n")], maxsize = 10, maxorderint = 1,
        maxsumofpow = 1, userseed=1900,silent=TRUE,vfold = 5, nsplits = 1,family=binomial,Dmove=FALSE
        ,Smove=FALSE)
    Q.L.t.DSA[[t0-t+1]] <- Q.DSA$model.selected
}

## Fit the initial model for Q(bar{L})(t)) (selected above or given as input by the user)
Q.L.t.glm <- glm(Q.L.t.DSA[[t0-t+1]],data = Q.L.t.data[,c(Ls.DSA,"Q.n")],family=binomial)

## Output the fitted model that defines the initial estimate of Q(bar{L})(t))
Q.L.t.DSA.out[[t0-t+1]] <- summary(Q.L.t.glm)$coef[,c(1,4),drop=FALSE]
Qnames.tmp <- row.names(Q.L.t.DSA.out[[t0-t+1]])
Q.L.t.DSA.out[[t0-t+1]] <- cbind("Estimate"=Q.L.t.DSA.out[[t0-t+1]][,1],"OR"=exp(Q.L.t.DSA.out[[t0-
    t+1]][,1]),"p value"=Q.L.t.DSA.out[[t0-t+1]][,2])
rownames(Q.L.t.DSA.out[[t0-t+1]]) <- Qnames.tmp
Q.L.t.DSA.out[[t0-t+1]] <- round(Q.L.t.DSA.out[[t0-t+1]],3)
Q.L.t.DSA.out[[t0-t+1]] <- cbind("Covariate"=gsub("_",".",rownames(Q.L.t.DSA.out[[t0-t+1]])),Q.L.t.
    DSA.out[[t0-t+1]])
Q.L.t.DSA.out[[t0-t+1]][("Intercept"),"OR"] <- ""

## Update the initial estimate of Q(bar{L})(t)) by weighted regression with offset
Q.L.t.offset <- predict(Q.L.t.glm,newdata=Q.L.t.data) # offset values
weights.update <- Q.L.t.data[, "unstabIPAW"] # unstabilized IP weights
if(truncate.level>0){ # truncate IPW=num/denom at truncate.level, i.e., unstabIPW=1/denom truncated
    at truncate.level/num
    cat("\nwith truncation")
    weights.update.truncated <- truncate.level/Q.L.t.data[,paste("numd",theta ,sep="")]
    weights.update <- ifelse(weights.update>weights.update.truncated ,weights.update.truncated ,weights
        .update)
}
## Logistic regression with offset and IP weights based on an intercept model
Q.L.t.tmle <- glm(Q.n ~ 1,family=binomial,offset=Q.L.t.offset,weights=weights.update,data=Q.L.t.
    data) # steps 3 and 4.b of Section 3.1.
## output updated estimator
Q.L.t.update.out[[t0-t+1]] <- summary(Q.L.t.tmle)$coef[,c(1,4),drop=FALSE]
Qnames.tmp <- row.names(Q.L.t.update.out[[t0-t+1]])
Q.L.t.update.out[[t0-t+1]] <- cbind("Estimate"=Q.L.t.update.out[[t0-t+1]][,1],"p value"=Q.L.t.
    update.out[[t0-t+1]][,2])
rownames(Q.L.t.update.out[[t0-t+1]]) <- Qnames.tmp
Q.L.t.update.out[[t0-t+1]] <- round(Q.L.t.update.out[[t0-t+1]],3)
Q.L.t.update.out[[t0-t+1]] <- cbind("Covariate"=gsub("_",".",rownames(Q.L.t.update.out[[t0-t+1]])),
    Q.L.t.update.out[[t0-t+1]])

```

```

## Predicted values for Q(bar{L}(t))
## for patients with a predicted value different from 1
Q.L.t.tmle.n <- 1/(1+exp(-(Q.L.t.offset+Q.L.t.tmle$coef)))
names(Q.L.t.tmle.n) <- Q.L.t.data[,"Study_ID"]
## for patients with known predicted value of 1
ids.failed.before.t.dtheta <- which(Odata[,"T.tilde"]<=(t-1) & Odata[,"DELTA"]%in%1 & Odata[,"period"]==Odata[,"T.tilde"] & Odata[,dtheta]%in%1)
Q.L.t.tmle.n.1 <- rep(1,length(ids.failed.before.t.dtheta))
names(Q.L.t.tmle.n.1) <- Odata[ids.failed.before.t.dtheta,"Study_ID"]
## create one vector with all predicted values
Q.L.t.tmle.n.extended[[t0-t+1]] <- c(Q.L.t.tmle.n,Q.L.t.tmle.n.1)

## algorithm above is iterated for decreasing t (i.e., t=t0, ..., 0)
t <- t-1
}

## Estimation of E( Q(L(0)) ), i.e. step 5 of Section 3.1
QY.L.t.data <- rep(NA,length(Odata[Odata[,"period"]%in%0,"Study_ID"]))
names(QY.L.t.data) <- Odata[Odata[,"period"]%in%0,"Study_ID"]
## group 1: patients who followed rule up to t=0
QY.L.t.data[ names(Q.L.t.tmle.n) ] <- Q.L.t.tmle.n
## group 2: patients who did not follow rule at t=0 (extrapolation)
idgroup2 <- names(QY.L.t.data)[is.na(QY.L.t.data)]
## two subgroups:
## subgroup 1 - patients with an indicator of failure at 1 before t=-1 while on dtheta (there should
## be no patient in this group)
if(!sum(idgroup2%in%names(Q.L.t.tmle.n.1))%in%0)stop("Pb")
## subgroup 2 - the other patients
data.extrap <- Odata[ Odata[,"Study_ID"]%in%idgroup2[!idgroup2%in%names(Q.L.t.tmle.n.1)] & Odata[,"period"]%in%0 , ]
Q.L.t.n.offset.group2 <- predict(Q.L.t.glm,newdata=data.extrap)
Q.L.t.tmle.n.group2 <- 1/(1+exp(-(Q.L.t.n.offset.group2+Q.L.t.tmle$coef)))
names(Q.L.t.tmle.n.group2) <- data.extrap[,"Study_ID"]
QY.L.t.data[ names(Q.L.t.tmle.n.group2) ] <- Q.L.t.tmle.n.group2
Q.L.t.tmle.n.extended[[t0+1]] <- c(Q.L.t.tmle.n.extended[[t0+1]],Q.L.t.tmle.n.group2)

## TMLE point estimate
TMLE.pt.est <- mean(QY.L.t.data)

return(list("Q.L.t.DSA"=Q.L.t.DSA,"Q.L.t.DSA.out"=Q.L.t.DSA.out,"Q.L.t.update.out"=Q.L.t.update.out,
           "TMLE.pt.est"=TMLE.pt.est,"Q.L.t.tmle.n.extended"=Q.L.t.tmle.n.extended))
}

#####
##### APPLICATION OF THE PREVIOUS ROUTINE #####
#####

library(multicore) # for parallel computing
TMLE.t0.11 <- mclapply(list(7,7.5,8,8.5),function(x,t0){
  res <- get.TMLE.pt.est(t0,theta=x)
  return(res)
},t0=11,mc.cores=10) # Derivation of the untruncated tmle for the 4 counterfactual cumulative risks at
# 3 years (quarters 0 to 11)
names(TMLE.t0.11) <- as.character(c(7,7.5,8,8.5))

### Display the four point estimates
TMLE.t0.11$"7"$"TMLE.pt.est"
TMLE.t0.11$"7.5"$"TMLE.pt.est"
TMLE.t0.11$"8"$"TMLE.pt.est"
TMLE.t0.11$"8.5"$"TMLE.pt.est"

```

A. 2. Influence curve

```

#####
##### ROUTINE TO DERIVE THE TMLE INFLUENCE CURVE #####
#####

### Arguments to provide to the routine:
### 't0' is the time point when the cumulative risk of interest is estimated
### 'theta' identifies the dynamic intervention of interest (7, 7.5, 8, or 8.5)
### 'TMLE.res' is the output from the 'get.TMLE.pt.est' routine above applied with the same 't0' and
### 'theta' values
### 'truncate.level' defines, when strictly positive, the truncation level for estimates of the IP
### weights. Estimates of the IP weights are left untruncated when a negative value is provided.

get.TMLE.IC <- function(t0,theta,TMLE.res,truncate.level=-1){


```

```

u.study.id <- Odata[Odata[, "period"]%in%0, "Study_ID"] # unique identifiers
n.sample <- length(u.study.id) # sample size n
IC <- as.data.frame(matrix(NA, nrow=(t0+2)*n.sample, ncol=3)) # data frame that will contain the t0+2
# values of D^*_{theta, t}(O_i) (see formula in Section 3.2) for each patient i and t=0,...,t0+1
colnames(IC) <- c("Study_ID", "period", "IC")
IC[, "Study_ID"] <- rep(as.character(u.study.id), each=(t0+2))
IC[, "period"] <- rep(0:(t0+1), n.sample)
theta <- as.character(theta)
dtheta <- paste("d", theta, sep="")
Qs <- TMLE.res[[theta]][["Q.L.t.tmle.n.extended"]] # predicted TMLE values for Q(bar{L}(t)) for t=t0
# ... , 0
QY <- Odata[Odata[, "period"]%in%(t0+1), Yname] # outcome values at t0+1
names(QY) <- Odata[Odata[, "period"]%in%(t0+1), "Study_ID"]
## add Y(t0+1)=1 for patients with T lower than or equal to t0 (I(T<=t0)=1)
id.event.before.or.at.t0 <- unique(Odata[Odata[, "DELTA"]%in%1 & Odata[, "T.tilde"]<t0, "Study_ID"])
QY2 <- rep(1, length(id.event.before.or.at.t0))
names(QY2) <- id.event.before.or.at.t0
QY <- c(QY, QY2)

QL0 <- rep(TMLE.res[[theta]][["TMLE.pt.est"]], length(u.study.id)) # predicted values for E( Q(L(0) ) ,
# i.e., the TMLE point estimate of the cumulative risk.
names(QL0) <- u.study.id

Qs <- c(list(QY), Qs, list(QL0)) # values for outcome Y(t0+1) and Q^theta
names(Qs) <- as.character((t0+2):0)

T.tilde <- Odata[Odata[, "period"]%in%0, "T.tilde"]
names(T.tilde) <- Odata[Odata[, "period"]%in%0, "Study_ID"]

IC.t <- as.data.frame(matrix(NA, nrow=n.sample, ncol=5)) # will contain for a given time point t, the
# building blocks needed to compute D^*_{theta, t}(O_i) for all patients i (see formula in Section
# 3.2).
colnames(IC.t) <- c("Q.t.1", "Q.t", "T.check", "I.d", "prod.g") # 'Q.t.1' and 'Q.t' will be the values
# for Q(bar{L}(t+1) and Q(bar{L}(t)), respectively. T.check will be the value for check{T}(t-1). I.
# d will be the value for I(bar{A}(check{T}(t-1)=d_theta(bar{L}(check{T}(t-1))))). prod.g will be
# the value for the inverse of the denominator of D^*_{theta, t}(O_i)
row.names(IC.t) <- u.study.id

for(t in 0:(t0+1)){ # computes for each t the values for D^*_{theta, t}(O_i) (see formula in Section
# 3.2)
    cat("\n:", t, "theta:", theta)
    IC.t.fill <- IC.t
    Q.t.1 <- Qs[[as.character(t+1)]]
    IC.t.fill[names(Q.t.1), "Q.t.1"] <- Q.t.1
    Q.t <- Qs[[as.character(t)]]
    IC.t.fill[names(Q.t), "Q.t"] <- Q.t
    IC.t.fill[names(T.tilde), "T.check"] <- sapply(T.tilde, function(x,y)min(x,y), y=t-1)
    if(t==0){
        ic.t <- IC.t.fill[, "Q.t.1"]-IC.t.fill[, "Q.t"]
        IC[IC[, "period"]==t, "IC"] <- ic.t
    }else{
        Id.prodg.data <- merge(Odata[, c("Study_ID", "period", dtheta, "unstabIPAW", paste("numd", theta, sep=""))], data.frame("Study_ID"=rownames(IC.t.fill), IC.t.fill)[, c("Study_ID", "T.check")])
        Id.prodg.data <- Id.prodg.data[ Id.prodg.data[, "period"]==Id.prodg.data[, "T.check"], ]
        IC.t.fill[, "I.d"] <- Id.prodg.data[, dtheta]
        IC.t.fill[, "prod.g"] <- Id.prodg.data[, "unstabIPAW"]
        if(truncate.level>0){
            cat("\nwith truncation")
            weights.update.truncated <- truncate.level/Id.prodg.data[, paste("numd", theta, sep="")]
            IC.t.fill[, "prod.g"] <- ifelse(IC.t.fill[, "prod.g"]>weights.update.truncated, weights.update.
            truncated, IC.t.fill[, "prod.g"])
        }
        ic.t <- ifelse(IC.t.fill[, "I.d"]%in%0, 0, IC.t.fill[, "I.d"]*IC.t.fill[, "prod.g"]*(IC.t.fill[, "Q.t.1"]
        "-IC.t.fill[, "Q.t"]))
        IC[IC[, "period"]==t, "IC"] <- ic.t
    }
}
IC <- tapply(IC[, "IC"], IC[, "Study_ID"], sum) # compute the values for the TMLE influence curve by
# summing D^*_{theta, t}(O_i) for each i over t.
return(IC)
}

```

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