

Comparison of Statistical Approaches Dealing with Time-dependent Confounding in Drug Effectiveness Studies

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Abstract

In longitudinal studies, if the time-dependent covariates are affected by the past treatment, time-dependent confounding may be present. For a time-to-event response, marginal structural Cox models (MSCMs) are frequently used to deal with such confounding. To avoid some of the problems of fitting MSCM, the sequential Cox approach has been suggested as an alternative. Although the estimation mechanisms are different, both approaches claim to estimate the causal effect of treatment by appropriately adjusting for time-dependent confounding. We carry out simulation studies to assess the suitability of the sequential Cox approach for analyzing time-to-event data in the presence of a time-dependent covariate that may or may not be a time-dependent confounder. Results from these simulations revealed that the sequential Cox approach is not as

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Conflict of Interest

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effective as MSCM in addressing the time-dependent confounding. The sequential Cox approach was also found to be inadequate in the presence of a time-dependent covariate. We propose a modified version of the sequential Cox approach that correctly estimates the treatment effect in both of the above scenarios. All approaches are applied to investigate the impact of beta-interferon treatment in delaying disability progression in the British Columbia Multiple Sclerosis cohort (1995 – 2008).

Keywords

bias (epidemiology); causality; confounding factors (epidemiology); epidemiologic methods; inverse probability weighting; longitudinal studies; models; survival analysis

1 Introduction

Longitudinal studies can include regular measurements of clinical symptoms and disease activity as covariates, and it is natural that the values may change over time. Since the predictive ability of baseline covariates may decrease over the follow-up time, consideration of the full history of these time-dependent covariates, rather than just the baseline covariates would be preferable¹. However, if these covariates are affected by previous treatment and predicts the future treatment decision and future outcome conditional on the past treatment exposure, then such covariates are popularly known as “time-dependent confounders”^{2,3}. If the causal effect of treatment is of interest, the estimated hazard ratio may be biased whether or not the time-dependent confounders are included as covariates in a time-dependent Cox model analysis^{2,4}. In the presence of time-dependent confounding, marginal structural Cox models (MSCM) are frequently used to estimate the causal effect of a time-dependent treatment exposure^{5,6}. Sometimes MSCM estimates are unstable due to use of variable inverse probability of treatment weights (IPTW)^{7–9}. The sequential Cox approach has been proposed as an alternative to the MSCM approach⁹.

In a previous simulation study, we showed that a simplified implementation of the sequential Cox approach (considering only baseline covariate adjustment) performed well compared to a Cox proportional hazards model fit with time-dependent exposure while adjusting for baseline confounders¹⁰. To the best of our knowledge, no attempt has been made to explore the appropriateness of the sequential Cox approach in adjusting for the effect of time-dependent confounding in a simulation setting.

To overcome the limitations of this approach revealed by our simulations, we also propose a modified version of the sequential Cox approach in this paper. The primary focus of this paper is to assess the performance of these sequential Cox approaches for dealing with a time-dependent confounder. A secondary aim of this paper is to examine how these methods perform in the presence of a time-dependent covariate which does not interact with the past treatment condition (i.e., is not a ‘time-dependent confounder’). To do this, we simulate survival data with time-dependent treatment exposure. Two different conditions are considered for simulation: (1) a time-dependent confounder is present, and (2) a time-dependent covariate is present along with a baseline covariate. To assess their suitability in an application, we apply these methods to investigate the impact of time-varying beta-

interferon treatment in delaying disability progression in subjects from the British Columbia Multiple Sclerosis (MS) database (1995–2008)^{11,12}.

The remainder of the paper is organized as follows. In the next section, we describe the notation and design of the simulation study, the methods used to address time-dependent confounding, and the metrics used to evaluate their performances. Then we summarize the simulation and the MS data analysis results. The paper concludes with a discussion of the results, and the implications and limitations of the current study.

2 Methods

2.1 Notation

Consider a hypothetical longitudinal study consisting of n subjects ($i = 1, 2, \dots, n$). Let $t_0 = 0$ be the start of follow-up or the time of the baseline clinic visit. Baseline covariates L_0 (binary or continuous) are recorded at baseline. Follow-up continues until the time of failure T or the time of censoring T^C . Let that, $[t_m, t_{m+1})$ constitutes the m -th interval (say, m -th month in the follow-up). At intervals $m = 0, 1, 2, \dots, K$, regular measurements of the binary treatment status A_m ($= 1$ for treated and 0 otherwise) are recorded. Let C_m be the binary indicator of censoring ($= 1$ if censored due to dropout or artificial censoring and 0 otherwise). Let $a_m = (a_0, a_1, \dots, a_m)$ be the observed realizations of the treatment history up to interval m , and similarly, let \tilde{L}_m and \tilde{C}_m be the observed realizations of the covariate history \tilde{L}_m and the censoring history \tilde{C}_m up to interval m respectively. The binary indicator of failure by time t_{m+1} is defined as $Y_{m+1} = I(T \leq t_{m+1})$. As the sequential Cox approach does not allow for treatment discontinuation, we assume that the subjects may initiate treatment at most once and that they continue on the treatment thereafter until the end of their follow-up. Let treatment initiation occur at time T^A .

2.2 Analysis Approaches

Brief characteristics of the analysis approaches are shown in Table 1. We describe these methods in detail in the following sections using the notation defined above.

2.2.1 Cox Model with Time-dependent Treatment and Covariates—In the presence of baseline confounders L_0 and time-dependent covariates L_m , one way to express the hazard function through the time-dependent Cox model is as follows:

$$\lambda(m|L_0, L_m) = \lambda_0(m) \exp \left(\tilde{\psi}_1 A_m + \psi_2 L_0 + \psi_3 L_m \right) \quad (1)$$

where m is the visit index, $\lambda_0(m)$ is the unspecified baseline hazard function, $\tilde{\psi}_1$ is the log-hazard ratio (log-HR) of the time-dependent treatment status (A_m), ψ_2 and ψ_3 are the vectors of log-HRs for the baseline covariates L_0 and the time-dependent covariates L_m , respectively.

2.2.2 Marginal Structural Cox Models—If the time-dependent covariate L_m is influenced by past exposure, i.e., if L_m is a time-dependent confounder, playing a dual role

as a confounder and an intermediate variable in the causal pathway between treatment and outcome, then ψ_1 as estimated from equation (1) may be biased² (i.e., may deviate from the target parameter ψ_1 ; discussed in detail in Web-Appendix §A). Instead of using L_m as a covariate, the MSCM approach uses it to calculate IPTW that are person-time specific measures of the degree to which L_m confounds the treatment selection process.

Stabilized inverse probability of treatment and censoring (IPTC) weight, sw_m , can be obtained by multiplying stabilized IPTW, sw_m^T , by stabilized inverse probability of censoring weights (IPCW), sw_m^C ⁵, where

$$sw_m^T = \prod_{j=0}^m \frac{pr(A_j=a_j | \bar{A}_{j-1}=\bar{a}_{j-1}, L_0=l_0)}{pr(A_j=a_j | \bar{A}_{j-1}=\bar{a}_{j-1}, L_0=l_0, \bar{L}_j=\bar{l}_j)}, \quad (2)$$

and

$$sw_m^C = \prod_{j=0}^m \frac{pr(C_j=0 | \bar{C}_{j-1}=\bar{c}_{j-1}, \bar{A}_{j-1}=\bar{a}_{j-1}, L_0=l_0)}{pr(C_j=0 | \bar{C}_{j-1}=\bar{c}_{j-1}, \bar{A}_{j-1}=\bar{a}_{j-1}, L_0=l_0, \bar{L}_{j-1}=\bar{l}_{j-1})}. \quad (3)$$

The weights sw_m are used in the time-dependent Cox model with hazard function modelled as follows to weight the contribution of each person-time observation so that the confounding due to L_m is removed:

$$\lambda(m|L_0) = \lambda_0(m) \exp(\psi_1 A_m + \psi_2 L_0), \quad (4)$$

where ψ_1 is log-HR of the time-dependent treatment status (A_m). Note that IPCW is used only if non-random censoring is present. When the numerators in equations (2) and (3) are replaced by 1, these become the unstabilized IPTC weights, w_m . We used pooled logistic regression^{2,5} to estimate the IPTC weights. Estimation procedure details are included in Web-Appendix §B.

2.2.3 Sequential Cox Approach—Suppose that at least one subject initiates treatment in the m -th interval $[t_m, t_{m+1})$. We want to mimic a randomized clinical trial for each such interval. The mini-trial corresponding to the m -th interval (hereafter referred to as the m -th mini-trial) involves only subjects who have not previously received any treatment. Among the subjects at-risk at t_m the subjects initiating treatment during the interval $(t_m < T^A < t_{m+1})$ are considered as the treated group, while the remaining subjects are considered as the control group. These control subjects are artificially censored at their times of later treatment initiation ($T^A > t_{m+1}$) to avoid confounding due to treatment. As these subjects are artificially censored, the analysis must be adjusted using IPCW.

In the analysis, we adjust for the baseline confounders L_0 measured at inclusion or baseline, the time-dependent covariates L_m measured at the start of the interval when patient started the treatment and the lagged covariates L_{m-1} consisting of the lagged value measured at the previous interval of the treatment start. Adjustment of these covariate values should help to reduce bias in the estimation of the treatment effect from the m -th mini-trial data⁹. Let us denote $\tilde{L}_m = (L_0, L_{m-1}, L_m)$. Here, L_0 includes the covariate values measured at baseline (i.e., time-static baseline covariates as well as the time-varying covariate or confounder value at time-point $m = 0$).

We assume that the different mini-trials may have different baseline hazard functions but all subjects in the same mini-trial have the same baseline hazard function. Under this assumption, use of a stratified Cox model is appropriate. Therefore, one way to model the hazard function for the m -th mini-trial is⁹:

$$\lambda^m(j|L_0, \bar{L}_j) = \lambda_{0m}(j) \exp \left(\vec{\psi}_1 A_j + \vec{\psi}_2 \tilde{L}_m \right); \quad j \geq m \quad (5)$$

where $\lambda_{0m}(j)$ is the unspecified baseline hazard function for stratum m , $\vec{\psi}_1$ is log-HR of the time-dependent treatment status and $\vec{\psi}_2$ is the vector of log-HRs for the time-dependent covariates \tilde{L}_m . This hazard function should be weighted by IPCW (equation (3)). It was suggested that the resulting estimate should bear a causal interpretation under the assumptions of no unmeasured confounders and correct model specification for the hazard ratio and the censoring weights⁹. We used Aalen's additive regression model^{9,13} to estimate the IPCW.

We can fit a stratified Cox model to the combined data of all mini-trials (pseudo-data), stratified by the treatment initiation time. Inclusion of the same subject more than once invalidates the SE obtained from the stratified weighted Cox analysis. Computationally demanding resampling methods are suggested^{9,13} to obtain a correct SE. We used a robust (sandwich) estimate instead to save computational time similar to other simulation studies^{14,15}. An illustrative data construction example is provided in Web-Appendix §C and the corresponding software implementation details are provided in Web-Appendix §D.

2.2.4 Modified Sequential Cox Approach—As each of the mini-trials mimics a clinical trial, we propose to analyze the mini-trial data accordingly. Each mini-trial is created based on a particular month of treatment initiation. These treatment initiation months are considered as the new baselines (new time-0) for the corresponding mini-trials. Note that the time-fixed covariates measured at the original baseline (i.e., L_0) are included in the analysis. For covariates that vary over time, we consider all the information from the new baseline to the study end-point to analyze the data, as we would do in a clinical trial setting. For example, time-varying covariate or confounder values collected at the interval of treatment start and onward (i.e., $L_m = (L_m, L_{m+1}, \dots, L_K)$ for the m -th mini-trial) are included in the model for adjustment¹⁶. Unlike the original proposal⁹, we do not use any time-dependent confounder (or time-dependent covariate) values prior to the new baseline for adjustment. Therefore, the hazard function for the m -th mini-trial can be expressed as:

$$\lambda^m(j|L_0, \bar{L}_j) = \lambda_{0m}(j) \exp(\psi'_1 A_j + \psi'_2 \bar{L}_m); \quad j \geq m \quad (6)$$

where ψ'_1 is log-HR of the time-dependent treatment status and ψ'_2 is the vector of log-HRs for the time-dependent covariates L_m . However, the process of creating the pseudo-population remains the same. The proposed changes occur only in the analysis stage.

Theoretically proving the equivalence of the target parameters ψ'_1 from equation (6) and ψ_1 from equation (4) is not easy, but we have provided a heuristic justification of such equivalence later based on a Monte Carlo experiment. In some context, additional techniques, such as, matching^{17,18} or use of propensity scores¹⁹ or adherence-adjustments¹⁶ may be useful to make the subjects within a mini-trial more comparable, but those approaches are not considered here.

2.3 Design of Simulation

We adopt the data generation process of Young et al.²⁰ to simulate survival times where time-dependent confounding is present. To simulate survival times with time-dependent covariates (none of which are time-dependent confounders), we adapt the permutation algorithm²¹. Descriptions of these algorithms are presented in Web-Appendices §E and §F respectively.

2.4 Simulation Specifications

In our Monte Carlo study, we generated $N = 1,000$ datasets with $n = 2,500$ subjects, each followed for up to $m = 10$ subsequent monthly visits for each setting under consideration. We set $\lambda_0 = 0.01$ (on a monthly scale) to represent a rare disease condition and $\lambda_0 = 0.10$ (on a monthly scale) for a more frequent disease condition. We discuss a brief description of the two simulations under consideration in Table 2. Below we provide the detailed specifications of the simulation scenarios.

2.4.1 Simulation - I—In our implementation of the algorithm²⁰, counterfactual failure time $T_{\bar{0}}$'s are sampled from an exponential distribution, with constant λ_0 rate of monthly events throughout the follow-up. The binary time-dependent confounder, L_m , is modelled by the following covariates: a binary covariate $I(T_{\bar{0}} < c)$, previous treatment status A_{m-1} , and the lagged variable L_{m-1} :

$$\begin{aligned} \text{logit}(p_L) &= \text{logit} \Pr(L_m = 1 | A_{m-1}, L_{m-1}, Y_m = 0; \beta) \\ &= \beta_0 + \beta_1 I(T_{\bar{0}} < c) + \beta_2 A_{m-1} + \beta_3 L_{m-1}, \end{aligned} \quad (7)$$

with associated parameters $\beta = (\beta_0, \beta_1, \beta_2, \beta_3) = (\log(3/7), 2, \log(1/2), \log(3/2))$, $c = 30$ and $Y_m = I(T_{\bar{0}} < t_m)$. Here, the time-dependent covariate L_m is moderately affected by prior treatment A_{m-1} ($\beta_2 = \log(1/2) = -0.3$).

We model binary treatment status at each stage A_m with the factors current symptom L_m , past symptom L_{m-1} , and previous treatment status A_{m-1} as

$$\begin{aligned} \text{logit}(p_A) &= \text{logit} Pr(A_m=1|L_m, A_{m-1}, L_{m-1}, Y_m=0; \boldsymbol{\alpha}) \\ &= \alpha_0 + \alpha_1 L_m + \alpha_2 L_{m-1} + \alpha_3 A_{m-1}, \end{aligned} \quad (8)$$

with associated parameters $\boldsymbol{\alpha} = (\alpha_0, \alpha_1, \alpha_2, \alpha_3) = (\log(2/7), 1/2, 1/2, 10)$. Current treatment status A_m is made heavily dependent on the previous treatment status A_{m-1} by setting a high parameter value ($\alpha_3 = 10$). That way, we emulate the situation where subjects switch to treatment at most once and keep on using the treatment without much interruption or discontinuation. The true causal effect parameter (i.e., treatment effect) is set to be $\psi_1 = 0.5$ (in equation (4)).

The equations (7) and (8) define L_m as a time-dependent confounder affected by prior treatment². In particular, past treatment exposure status A_{m-1} affects the time-dependent confounder L_m , which then predicts future treatment exposure A_m . L_m is also associated with the future failure status Y_{m+1} via $I(T_0 < c)$. Here, T_0 is the untreated counterfactual survival time and c is an arbitrary cut-point used to generate the binary variable $I(T_0 < c)$. The value of c affects the degree of variability in the indicator variable $I(T_0 < c)$ ²². Without $I(T_0 < c)$, there would not be any confounding in the exposure-outcome relationship. The confounding here arises via the path: $Y_{m+1} \leftarrow I(T_0 < c) \rightarrow L_m \rightarrow A_m$. This indicator variable $I(T_0 < c)$ therefore dictates the degree to which T_0 affects L_m for a chosen value of c .

2.4.2 Simulation - II—We assume an exponential distribution for generating failure times T with constant $\lambda_0 = 0.01$ rate of monthly events throughout the follow-up. A uniform distribution $U(1, 60)$ months is assumed to generate censoring times T^C ; i.e., administrative censoring is set at 5 years of follow-up. Treatment initiation time T^A is generated from a uniform distribution $U(0, 10)$ (in months). Additionally, we consider sex as a baseline confounder in these data. A subject's sex is generated based on a Bernoulli distribution where the probability of being male is 0.3. We also add one time-dependent confounder L_m , which could represent cumulative disease activity, for example, such that higher cumulative disease activity has a higher risk (a log-HR of $\psi_3 = \log(1.5)$). This time-dependent confounder L_m is generated based on a Bernoulli distribution where the probability of disease activity increment is 0.75, accumulating the disease activity over at most $m = 10$ periods of time.

The permutation algorithm²¹ is used to generate survival data where binary treatment A_m is time-dependent but the confounder L_0 is fixed at its baseline value. Arbitrarily, the effect parameters for treatment and sex on the survival outcome are set such that the treatment has a harmful effect (a log-HR of $\psi_1 = 0.5$) and males are at a lower risk than females (a log-HR of $\psi_2 = -0.7$).

2.5 Performance Metrics

We assessed the performance of the various approaches by the following measures:

- Bias = $\sum_{i=1}^N (\hat{\psi}_{1i} - \psi_1) / N$: The average difference between the true and $N = 1,000$ estimated parameters (log-HR).
- SD = $\sqrt{\sum_{i=1}^N (\hat{\psi}_{1i} - \bar{\psi}_1)^2 / (N-1)}$ where $\bar{\psi}_1 = \sum_{i=1}^N \hat{\psi}_{1i} / N$
- Model-based SE: The average of $N = 1,000$ estimated standard errors of the estimated causal effect.
- Coverage probabilities of model-based nominal 95% CIs: Proportion of $N = 1,000$ datasets in which the true parameter is contained in the nominal 95% CI.

The above quantities were defined in terms of MSCM parameter ψ_1 from equation (4). In order to define the same measures from other analysis approaches under consideration, we assumed that the true target parameters (defined in equations (1), (4) and (6) respectively) are the same for all approaches, e.g., $\tilde{\psi}_1 = \psi_1 = \psi'_1 = 0.5$. A heuristic justification of such assumption of equivalence is provided at the section ‘Marginal versus Conditional Interpretations’.

3 Simulation Results

3.1 Description of the Simulated Data

To describe the data obtained from the simulation settings under the rare event condition, we generated datasets with a larger number of subjects (25,000) with up to 10 subsequent visits from each simulation algorithm. The characteristics of the treated, untreated and partially treated groups, their failure rates and average number of visits are listed in Table 3.

3.2 Rare Event Condition

We present the results from the rare event condition ($\lambda_0 = 0.01$ in a monthly time-scale) in the two simulation settings.

3.2.1 Results From Simulation-I—Results from simulation-I are reported in Table 4. MSCM with treatment status (A_m) is fitted to validate the data generating algorithm. The corresponding stabilized weights are generated based on the relationship between treatment status (A_m) and the time-dependent confounder L_m . The level of bias is negligible compared to other approaches under consideration and the average coverage probability of the model-based nominal 95% CIs is 0.942. These results are now considered as the ideal for comparison purposes for this simulation setting. The time-dependent Cox models provide biased estimates (assuming $\tilde{\psi}_1 = \psi_1 = 0.5$) in the presence of this time-dependent confounder. The average coverage probability of the model-based nominal 95% CIs for the method is very low. The bias of sequential Cox analysis is comparable to that with the time-dependent Cox analysis, while the corresponding effect estimates are considerably more variable. The properties of the modified sequential Cox approach, on the other hand, are comparable to that of MSCM. The corresponding average coverage probability of the model-based nominal 95% CIs for the method is comparable to that with MSCM.

3.2.2 Results From Simulation-II—Results from simulation-II are reported in Table 5. The time-dependent Cox model with treatment status (A_m), baseline covariate (L_0) and time-dependent covariate (L_m) is fitted to validate the data generating permutation algorithm. The level of bias is negligible and the average coverage probability of the model-based nominal 95% CIs is 0.952. These results are considered as the ideal for comparison purposes for this simulation setting. When the sequential Cox approach is used in this simulation setting, we observe some bias. We apply MSCM with L_m treated as a time-dependent confounder, even though L_m is only a time-dependent covariate that is not affected by the past treatment. The corresponding bias is negligible and the average coverage probability of the model-based nominal 95% CIs is 0.952. As L_m is not a time-dependent confounder in this simulation, the similarity between the estimates obtained from MSCM and the time-dependent Cox model is not surprising. The properties of the modified sequential Cox approach are again comparable to MSCM with reasonable average coverage probability of the model-based nominal 95% CIs.

3.3 Marginal versus Conditional Interpretations

We need to take into account the different interpretations of the target quantities ($\tilde{\psi}_1$, ψ_1 and ψ'_1 from equations (1), (4) and (6) respectively) being estimated by the three approaches under consideration. The clinical context should dictate whether the target parameter should bear a marginal or conditional interpretation. Conditional interpretations are generally useful in deciding personalized drug choices, whereas marginal interpretations may be more useful in making generalized policy decisions for a heterogeneous group of patients¹⁵.

The modified sequential Cox approach and its proposed modification emulate a sequence of conditionally randomized treatment assignments. This is done by first reorganizing the observed data and then stratifying the combined data based on the month of treatment initiation, conditioning on the pre-treatment covariate values. The estimated ψ'_1 from a modified sequential Cox approach (as well as estimated ψ_1 from a sequential Cox approach), therefore, bears a conditional interpretation^{9,13}, as does the estimated log-hazard ratio $\tilde{\psi}_1$ from a time-dependent Cox model^{23,24}.

In contrast, MSCM estimates the log-hazard ratio ψ_1 between two counterfactual scenarios: all subjects are treated at a given time versus none of the same subjects are treated at that time. The target quantity of interest ψ_1 estimated from MSCM is the causal effect of the treatment. Assuming the MSCM assumptions hold, this quantity should match the estimated treatment effect from a randomized clinical trial^{25,26}. In that sense, the MSCM approach mimics randomized clinical trial data setting by appropriately weighting observational data. As the corresponding outcome or hazard model does not condition on any time-dependent covariates that affect future treatment, the log-hazard ratio estimated from a MSCM is a marginal or population-averaged quantity²⁷. It is possible to extend the MSCM by incorporating baseline covariates in the hazard model²⁸. When we use stabilized weights in a MSCM, the treatment effect is marginal with respect to the time-dependent confounders, but conditional with respect to the baseline covariates^{11,29,30}.

Comparing the MSCM target parameter estimate with any conditional treatment effect estimate (from time-dependent Cox model approach: which is considered as the standard for comparison in simulation - II) is not straightforward when noncollapsible measures, such as HR or OR, are employed^{30–34}. Establishing the equivalence of the target parameters (log-hazard ratios $\tilde{\psi}_1$, ψ_1 and ψ'_1 from equations (1), (4) and (6) respectively) from the approaches under consideration may not be easy. However, the difference between the conditional and marginal parameters is expected to be negligible when the event rate in the time-intervals under consideration is small^{14,33}. In our simulations, the event rate was 1% in each month-interval. In this scenario, noncollapsibility of the HRs should not have any noticeable impact on the findings. We performed the following numerical experiment to support this proposition^{14,15}. We generated a very large cohort ($n = 100,000$) under the simulation - II settings. As expected, the time-dependent Cox model and MSCM yield almost identical values of the treatment effect estimates (log-hazard ratio of $\hat{\psi}_1 = 0.5084$ versus $\hat{\psi}_1 = 0.5091$). This further provides some evidence that non-collapsibility of the HR does not affect our simulation - II findings.

Similarly, we performed another Monte Carlo experiment for the simulation – I setting with $N = 100$ larger cohorts ($n = 100,000$) to investigate whether ψ'_1 and ψ_1 quantities estimated via the modified sequential Cox and MSCM respectively (which is considered as the standard for comparison in simulation - I) differed systematically in the settings we investigated. Both approaches produce very similar values of the treatment effect estimates on average (see Table 6). For this setting, this shows that the target parameters for these two approaches are not materially different. To check the adequacy of the sample size $n = 2,500$ chosen in our original simulation – I, this study is also repeated for other cohort sizes $n = 5,000, 10,000$ and $50,000$ (see Table 6). The results look very similar, and expectedly the SDs are decreasing with increment of sample sizes.

3.4 When More Events are Available

The trends in the bias from the more frequent event condition ($\lambda_0 = 0.1$ in a monthly time-scale) are similar compared to those in the rare event condition (see Web-Tables H.1–H.2). As expected, the standard errors are much less than in the corresponding analyses when failure rates are rare. Bias is slightly lower in some cases. One noticeable difference is observed in simulation setting - I: in the presence of the time-dependent confounder, when the failure rate is more frequent, the bias of the time-dependent Cox and MSCM approaches is reduced to minimal levels, whereas considerable bias is still apparent with the sequential Cox approach. On the other hand, the average coverage probability of the model-based nominal 95% CIs from the time-dependent Cox approach is smaller than that of MSCM. The modified sequential Cox approach estimates are still associated with good statistical properties.

4 Application in Multiple Sclerosis

We apply these methodologies to the British Columbia (BC) MS cohort data (1995–2008)¹¹. The dataset was used in previous studies^{11,12,35–38} to estimate the effect of β -IFN on time to irreversible disability outcomes. As before, irreversible progression of disability is measured

by sustained expanded disability status scale (EDSS) 6 which is confirmed after at least 150 days, with all subsequent EDSS scores being 6 or greater. Web-Appendix §G describes the baseline characteristics, eligibility and exclusion criteria of the MS cohort.

Potential baseline confounders L_0 include age, sex, disease duration and EDSS score. Also, we consider the cumulative number of relapses in the previous 2 years (hereafter called ‘cumulative relapses’) as a time-dependent confounder L_m ¹¹. Once the subjects initiate β -IFN, we assume they continue taking the drug without any discontinuation until they develop the outcome or are censored, as is assumed in our simulations and previous pharmacoepidemiologic studies^{9,13,39}. As found in the previous study¹¹ using this cohort, we consider the MSCM estimates to be ideal in this time-dependent confounding context. Results are reported in Table 7.

The IPCWs in the modified sequential Cox approach are less variable than the IPWs in MSCM. IPCWs are estimated separately for each mini-trial⁹. When they are estimated from the aggregated dataset instead⁸, or when IPCWs were estimated via pooled logistic regression models^{2,5,39}, the HR estimates are very similar (see Web-Appendix §I). No matter how they are constructed, the IPCWs from the mini-trials are well-behaved, i.e., the averages are close to one and they have low variability (most are within the range of 0.9 to 1.1 and the distributions are unimodal and symmetric; see Web-Figures I.1 and I.2).

5 Discussion

In observational studies, the estimation of a treatment effect is challenging in the absence of randomization. In longitudinal studies, additional complexity arises in the presence of time-dependent confounding. MSCMs are popularly used to deal with this problem in the survival analysis setting. MSCMs handle time-dependent confounding by re-weighting the data in such a way that the confounding effect of the time-dependent confounder is removed. Then adjusting for the baseline confounders (but not the time-dependent confounder) in the re-weighted pseudo-population is adequate to obtain the counterfactual or causal effect of the treatment under the identifiability conditions^{8,28}. Sometimes, the MSCM estimates may be unstable due to use of IPTWs and an alternate analysis or view of the data may be helpful.

The sequential Cox approach was proposed as an alternative method to the MSCMs for estimation of the treatment effect from complex observational data settings where the treatment is time-dependent and censoring may be non-random⁹. This approach restructures the data in such a way that a sequence of subsets of data (mini-trials) are created based on intervals of treatment initiation. Aggregation of all the mini-trial data produces the pseudo-population. In this pseudo-population, subjects initiating treatment at each interval are compared to those who do not initiate treatment, conditional on covariates at respective intervals as well as baseline covariates. Although IPTWs are avoided in the sequential Cox approach, IPCWs are still required. These weights are less variable and more stable than IPTWs^{7,9} and appropriately handle the artificial censoring at later treatment start dates. We proposed a modified version of this approach that deal with analyses differently than the original proposal.

The treatment effect that is estimated from a MSCM is a marginal estimate as it is obtained by averaging over subjects with different hazards. This estimate does not condition on the time-dependent confounder. Rather the time-dependent confounder plays a role in creating weights for the MSCM model fitting. These weights are used to create the pseudo-data which is free from time-dependent confounding and mimics a clinical trial situation. Similarly, the sequential Cox approach contrasts subjects within mini-trials, where each mini-trial includes subjects who did and did not initiate the treatment. Controlling for current values of the time-dependent covariates as well as baseline confounders should make the treated subjects conditionally exchangeable with control subjects at the time of treatment initiation. Within each mini-trial, treatment assignment could be considered as random among the comparable subjects.

While the MSCM approach provides a marginal estimate of the treatment effect, the sequential Cox approach and its modified version provide conditional estimates. Both approaches are equipped to adjust for baseline confounders. Although the mechanisms and interpretations behind the sequential Cox approach and MSCM are different, both claim to achieve the same goal of estimating the causal effect of treatment in the presence of time-dependent confounders. Generally marginal and conditional estimates may not be directly comparable due to non-collapsibility^{9,15}. By examining whether these quantities differed systematically in the settings investigated, we showed that the use of non-collapsible measure has not been an issue in the specific simulation settings we considered.

To the best of our knowledge, ours is the first study to use simulation studies to investigate the characteristics of a sequential Cox approach that has been suggested as being suitable in the context of time-dependent confounding. The first simulation setting (simulation-I) deals with the situation where the time-dependent covariate is affected by the prior treatment (i.e., is a time-dependent confounder). When a time-dependent confounder is present, MSCM is known to be an appropriate method and hence results from this method are used as the standard for comparison in this simulation setting. In this simulation process, we generate data such that the time-dependent confounder dictates the treatment assignment in the following periods. Among the subjects selected for a mini-trial based on those initiating treatment or at risk in a given period, only current (and lagged) values of the time-dependent covariates are used as adjustments in the sequential Cox approach. We proposed a modified version of sequential Cox approach, based on controlling for the time-dependent variable (confounder or covariate) values after the treatment initiation. We investigated via simulation whether such adjustments are sufficient. In the second setting (simulation-II), we have a baseline covariate and a time-dependent covariate. As the time-dependent Cox model is appropriate for simulation setting II, we use these results as the standard for comparison.

Previously, the sequential Cox approach was shown to work very well in comparison to the time-dependent Cox approach in the absence of any time-varying covariate or confounder¹⁰. However, we do not find the sequential Cox approach to be as effective as MSCM when a time-dependent confounder is present (simulation-I) or even when a time-dependent covariate which is not a time-dependent confounder is present (simulation-II). The sequential Cox approach does not seem to remove the effects of time-dependent confounding adequately, especially when the event rate is small. Based on our simulation

findings, when we need to consider time-dependent confounders in order to adequately model a disease process, we recommend the use of the MSCM approach or the modified sequential Cox approach, as both are capable of producing estimates of the treatment effect that are close to the MSCM target parameter ψ_1 .

We apply the methods under consideration to estimate the effect of β -IFN on disease progression. The modified sequential Cox approach produces effect estimate similar to MSCM. A sensitivity analysis of the sequential Cox approach without using IPC weights yielded very similar results, implying little impact of artificial censoring due to later treatment initiation.

The focus for the sequential Cox approach and its modified version is on recreating the covariate process at each treatment start using the mini-trial approach⁷. Such focused and detailed scrutiny could yield insights about the data which may be hard to extract using a MSCM approach. For example, the data associated with a given mini-trial can be extracted and separated quite easily from the combined mini-trial data (pseudo-population), it is straightforward to compare the effects of early versus late treatment initiation. It is also possible to estimate the treatment effect for patients with a specific level of a time-dependent covariate at treatment initiation. Variance estimation is a challenge in the sequential Cox and similar methods¹⁵. To account for possible multiple entry of the same control subjects in different mini-trials, we used a robust (sandwich) estimator. In our simulation studies, the average standard errors are slightly lower than the empirical standard deviations in most cases for the sequential Cox approach. However, for the modified version, these estimates are very close. For more accurate estimate of the standard errors, bootstrap or jackknife estimates could be used^{9,13}. Unlike our simulation settings, if the time-dependent covariates are very strongly affected by the prior treatment, further adjustments^{16–19} may be necessary. Using the same simulation scheme used in this study, future studies could assess the adequacy of the sequential Cox approaches and other similar methods^{17,27,40,41} under such extreme setting.

Similar to other simulation studies, we investigated a few possible scenarios. However, the assumptions underlying our data simulation are consistent with patterns typical in observational survival studies where associated covariates are measured regularly. For more complex disease scenarios where an investigator may wish to assess different treatment strategies (i.e., switching between therapies) over the course of time, our assumption of no discontinuations or interruptions in the treatment is restrictive and may not be suitable⁸. Further simulation studies are required to assess the effect on the precision of the estimates when varying the sample size of the simulated data as well as the number of simulated datasets generated from the algorithms considered in this study⁴². Future research could focus on analytical derivation of the effect estimates from the sequential Cox approach and its modified version in an effort to theoretically justify the proposed analysis roadmap.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of the Cox models used in the approaches under consideration.

Approach	Stratified	Time-dependent covariate history	Weight adjusted
TD-Cox	No	Full	No
MSCM	No	Full	Yes, IPTC [#]
Sequential Cox [‡]	Yes	Up to the new baseline [‡]	Yes, IPC [§]
Modified Sequential Cox [‡]	Yes	New baseline and afterwards ^{‡‡}	Yes, IPC [§]

TD-Cox, Cox model with time-dependent exposure; MSCM, Marginal structural Cox model; IPT, Inverse probability of treatment; IPC, Inverse probability of censoring; IPTC, Inverse probability of treatment and censoring.

[‡]For the sequential Cox approach, covariate values are collected at three time points for each mini-trial: at baseline, at the interval of treatment start and at the previous interval (the lagged value): $\tilde{L}_m = (L_0, L_{m-1}, L_m)$. Here, time-fixed covariates collected at the original baseline (i.e., L_0) are included in the analysis.

^{‡‡}For the modified sequential Cox approach, the time-dependent covariate values are collected at the new baseline and then at subsequent intervals (i.e., $\tilde{L}_m = (L_m, L_{m+1}, \dots, L_K)$). Time-fixed covariates collected at the original baseline (i.e., L_0) are also included in the analysis.

[‡]Robust (sandwich) estimate is used to obtain SEs.

[#]Pooled logistic regression is used to estimate the IPTC weights.

[§]Aalen's additive regression model is used to estimate the IPCW.

Table 2

Two simulation settings under consideration.

	Simulation - I	Simulation - II
Algorithm	20	21
Time-varying treatment	Yes	Yes
Baseline covariate	No	Yes
Time-varying covariate	No	Yes
Time-varying confounder	Yes	No

Table 3

Characteristics of the simulation settings under consideration.

Rates	Simulation-I	Simulation-II
Failure	0.143	0.084
Always treated	0.261	0.051
Never treated	0.046	0.150
Partially treated	0.692	0.799
Discontinuation	0.001 [†]	-
Mean visits	9.367	8.943

[†]Simulation-I allows a few exceptions (19 out of 25, 000) where there are discontinuations. However, the proportion of discontinuation in the simulation-I dataset is negligible (0.00076) and we do not expect any noticeable impact in the results due to this small number of exceptions.

Table 4

Comparison of the analytical approaches to adjust for time-dependent confounding from simulation-I (one time-dependent confounder and time-dependent treatment exposure) of 1, 000 datasets, each containing 2, 500 subjects followed for up to 10 time-intervals.

Approach	Bias	SD	se	Coverage Probability
TD-Cox [§]	0.438	0.168	0.169	0.251
Sequential Cox ^{#, †}	0.451	0.280	0.267	0.636
Modified Sequential Cox ^{*, @}	0.015	0.221	0.222	0.956
MSCM [‡]	0.029	0.201	0.205	0.942

TD-Cox, Cox model with time-dependent exposure; MSCM, Marginal structural Cox model.

[§]Includes the time-dependent confounder L_M as a covariate. In the presence of a time-dependent confounder, the time-dependent Cox model is not appropriate but the results are retained for comparison purposes.

[#]Adjusts for \tilde{L}_M .

[†]For the stabilized IPCWs, the numerator model adjusts for A_M , while the denominator model adjusts for A_M and \tilde{L}_M via Aalen's additive regression.

^{*}Adjusts for lagged values of A_M , the time-dependent confounder \tilde{L}_M , and lagged values of \tilde{L}_M . Note that, baseline covariates are not present in this setting.

[@]For the stabilized IPCWs, the numerator model adjusts for A_M , while the denominator model adjusts for A_M , \tilde{L}_M and lagged values of \tilde{L}_M via Aalen's additive regression.

[‡]The stabilized IPTW numerator model adjusts for time index and lagged values of A_M , while the denominator model additionally adjusts for current and lagged values of L_M to predict future treatment status via pooled logistic models.

Table 5

Comparison of the analytical approaches to adjust for time-dependent covariate from simulation-II (one baseline covariate, one time-dependent covariate and time-dependent treatment exposure) of 1, 000 datasets, each containing 2, 500 subjects followed for up to 10 time-intervals.

Approach	Bias	SD	se	Coverage Probability
TD-Cox [§]	0.000	0.164	0.162	0.952
Sequential Cox ^{#, †}	0.271	0.189	0.184	0.688
Modified Sequential Cox ^{*, @}	-0.022	0.231	0.234	0.961
MSCM ^{±, ‡}	-0.001	0.163	0.162	0.952

TD-Cox, Cox model with time-dependent exposure; MSCM, Marginal structural Cox model.

[§]The baseline covariate L_0 and time-dependent covariate L_M are included.

[#]Adjusts for L_0 and \tilde{L}_M .

[†]In the stabilized IPCW model, the numerator model adjusts for A_M and L_0 , while the denominator model adjusts for A_M , L_0 and \tilde{L}_M via Aalen's additive model.

^{*}Adjusts for baseline covariates L_0 , lagged values of A_M , the time-dependent confounder \tilde{L}_M , and lagged values of \tilde{L}_M .

[@]For the stabilized IPCWs, the numerator model adjusts for A_M and baseline variable L_0 , while the denominator model adjusts for L_0 , A_M , \tilde{L}_M and lagged values of \tilde{L}_M via Aalen's additive regression.

[±]Adjusts for only L_0 .

[‡]For the stabilized IPTWs, the numerator model adjusts for the time index, L_0 and lagged values of A_M , while the denominator model additionally adjusts for current and lagged values of L_M to predict future treatment status via pooled logistic models.

Table 6

Series of Monte Carlo studies for the simulation – I setting, each simulation with larger cohorts.

Approach	Bias (SD) from N = 100 cohorts			
	n = 5,000	n = 10,000	n = 50,000	n = 100,000
MSCM	0.013 (0.150)	0.007 (0.107)	0.011 (0.049)	0.003 (0.033)
Modified Sequential Cox	0.011 (0.157)	0.003 (0.100)	0.004 (0.048)	-0.001 (0.037)

Table 7

Summary of the estimated parameters from the multiple sclerosis (MS) patients' data from British Columbia, Canada (1995–2008).

Approach	\widehat{HR}	$se(\widehat{HR})$	95% CI	Weights	
				Average (SD)	range
TD-Cox [§]	1.29	0.23	0.91 – 1.82		
Sequential Cox ^{#, †}	1.23	0.32	0.74 – 2.07	1.00 (0.01)	0.74 – 1.63
Modified Sequential Cox ^{*, @}	1.36	0.26	0.93 – 1.99	1.00 (0.01)	0.92 – 1.24
MSCM ^{±, ‡}	1.31	0.23	0.92 – 1.84	1.00 (0.06)	0.37 – 1.60

TD-Cox, Cox model with time-dependent exposure.

[§] Adjusts for baseline covariates L_0 (sex, EDSS score, age and disease duration), and for the time-dependent confounder L_M 'cumulative relapses'.

[#] Adjusts for L_0 , A_M and \vec{L}_M .

[†] The stabilized IPCW numerator model adjusts for A_M and L_0 , while the denominator model additionally adjusts for L_M and lagged values of L_M via Aalen's additive model.

^{*} Adjusts for baseline covariates L_0 , lagged values of A_M , the time-dependent confounder \vec{L}_M and lagged values of \vec{L}_M .

[@] For the stabilized IPCWs, the numerator model adjusts for A_M and baseline variable L_0 , while the denominator model adjusts for L_0 , A_M , \vec{L}_M and lagged values of \vec{L}_M via Aalen's additive regression.

[±] Adjusts for the potential baseline confounders L_0 .

[‡] The stabilized IPTW numerator model adjusts for a restricted cubic spline of the follow-up time-index, baseline confounders L_0 and lagged values of A_M to predict future treatment status. The denominator model additionally adjusts for the current and lagged values of cumulative relapses (L_M) via the pooled logistic models.