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Assessing potentially time-dependent treatment effect from clinical trials and observational studies for survival data, with applications to the Women's Health Initiative combined hormone therapy trial

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Abstract

For risk and benefit assessment in clinical trials and observational studies with time-to-event data, the Cox model has usually been the model of choice. When the hazards are possibly non-proportional, a piece-wise Cox model over a partition of the time axis may be considered. Here we propose to analyze clinical trials or observational studies with time-to-event data using a certain semiparametric model. The model allows for a time-dependent treatment effect. It includes the important proportional hazards model as a sub-model, and can accommodate various patterns of time-dependence of the hazard ratio. After estimation of the model parameters using a pseudo-likelihood approach, simultaneous confidence intervals for the hazard ratio function are established using a Monte Carlo method to assess the time-varying pattern of the treatment effect. To assess the overall treatment effect, estimated average hazard ratio and its confidence intervals are also obtained. The proposed methods are applied to data from the Women's Health Initiative. To compare the WHI clinical trial and observational study, we use the propensity score in building the regression model. Compared to the piece-wise Cox model, the proposed model yields a better model fit and does not require partitioning of the time axis.

Keywords

average hazard ratio; censored data; hazard ratio; nonproportional hazards; semiparametric analysis; simultaneous inference

1. Introduction

Observational studies (OSs) and randomized controlled trials (RCTs) are the two major tools in assessing benefits or risks of pharmaceutical treatment and behavioral interventions.

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RCTs are considered the gold standard and are typically carried out at a confirmation stage of a research program. A random treatment allocation ensures that treatment status will not be confounded with either measured or unmeasured baseline characteristics. Thus the effect of treatment on outcomes can be estimated by directly comparing outcomes between treated and untreated subjects. However, with low event rates for many diseases, it may take a very large sample and lengthy follow-up time to ensure adequate power. These factors, in addition to the usual careful protocol development and monitoring of outcomes and adverse events, make RCT logistically challenging and expensive. An OS may be much less expensive and thus more feasible, and is often used at an exploratory stage. However, since investigators have no control over the treatment assignment, large discrepancies may exist in covariate distributions between the treatment groups. These discrepancies could lead to potentially biased estimates of treatment effects, making it difficult to ensure the reliability of the study results.

Sponsored by the National Heart, Lung, and Blood Institute, the Women's Health Initiative (WHI) randomized, placebo controlled estrogen plus progestin trial started in 1993. It was a trial of daily use of 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate based on a hypothesized reduction in coronary heart disease incidence. Few other research reports can match the high level of public response and expert discussion that the WHI trial generated. Contrary to the results from a substantial body of OSs, the WHI estrogen plus progestin RCT found an elevation in coronary heart disease risk over a 5.6-year intervention period through July 7, 2002 [1, 2]. This departure from expectation prompted researchers to hypothesize flaws in the WHI trial [3, 4] and to argue about lack of relevance of the trial results to important groups of combined hormone therapy users [5]. There was also speculation on reasons for a discrepancy between WHI trial results and related observational research, such as confounding in OSs, the limited ability of OSs to assess short-term effects, differences among combined hormone therapy preparations, and differences among the populations of women studied [6-8].

An important feature of the WHI RCT design was the inclusion of a companion OS involving 93,676 postmenopausal women (age 50-79 years). Participants were drawn from essentially the same catchment population, over the same time period, for the RCT and the OS. Many elements of the protocol and procedures were common to the two WHI components, including multiple baseline questionnaires, interview data collection, and major elements of outcome ascertainment. Thus the WHI provides an excellent setting for understanding and resolving the discrepancies between the RCT and OS results.

Prentice et al. [9] analyzed data from this WHI trial. The estrogen-plus-progestin hazard ratio estimates for coronary heart disease, stroke, and venous thromboembolism in the OS were 39-48% lower than those in the RCT following age adjustment. To adjust for confounding, various factors such as established cardiovascular disease risk factors, and various behavioral, dietary, and physical activity baseline measures were used in Cox regression analyses [10] of the results. The estimated estrogen-plus-progestin hazard ratios in the OS increased after the adjustment, but remained 30-38% lower than in the RCT. It was observed that the RCT hazard ratios tended to decrease with increasing time since initiation of estrogen-plus-progestin use, and that the OS hazard ratios were heavily

weighted by longer-term use while the RCT hazard ratios reflected shorter-term use. To control for both confounding and time since estrogen-plus-progestin initiation, piece-wise Cox regression models were used assuming constant hazard ratio for less than 2 years, 2-5 years, and more than 5 years since treatment initiation. As a result, hazard ratio estimates from the WHI RCT and OS were rather similar, although there was evidence of some remaining difference for stroke. Prentice et al. [9] discussed the implications of such analyses for the design and analysis of OS's when the hazard ratio of interest varies with time, and estimation of the hazard ratio as a function of time, from which average hazard ratio over certain time period can be calculated.

Here, we propose a new approach to assess potentially time-dependent treatment effects and apply it to the WHI RCT and OS data on combined post-menopausal hormone therapy. Instead of the piece-wise Cox regression model, we use a model that can accommodate differing short-term and long-term hazard ratios. This model includes the important proportional hazards model as a sub-model, and can accommodate various patterns of the time-dependence of the hazard ratio. There is no need to consider if or how the time axis should be partitioned for a piece-wise Cox model should the hazard ratio be time-dependent. As will be shown, different cut-off points in the piece-wise Cox model approach could lead to somewhat different results. It is possible to adaptively select the cut-off points [11]. In those approaches typically for identifiability it is assumed that the cut-off points exist. Alternative to the piece-wise Cox model, a defined time-varying covariate can also be used in a Cox regression model, resulting in a parametric form for the hazard ratio function [12, Ch. 6]. In comparison, we will see that the model used here expresses the hazard ratio function semiparametrically, and is comparatively more flexible and robust. In the literature, varying coefficient models are often used to describe the temporal effect of covariates and offer another option [13, 14]. Note that in those models, for the important two-sample case it becomes a purely nonparametric approach. Other approaches in dealing with time-dependent effects include analysis of the average hazard ratio [15] via weighted Cox regression [16] and analysis of the average regression effect [17] under non-proportional hazards, among others.

To visualize the time-dependence of the treatment effect, we will construct point-wise and simultaneous confidence intervals of the hazard ratio. When the hazard ratio is time-dependent, the hazard ratio being less than 1 at a particular point does not necessarily imply that the survival probability of the treatment group is greater than that of the control group at that point. But if the hazard ratio stays less than 1 from time zero up to a time point t_0 , for example, then the survival probability of the treatment group is greater than that of the control group for any $t < t_0$ (provided that censoring rates do not differ by treatment assignment or modeled covariates). Simultaneous confidence intervals, or confidence bands, provide important tools for assessing if the hazard ratio is less than 1 or greater than 1 over the entire data range or a particular part of the range. For a summary measure of the treatment effect, we use the average hazard ratio which is also used in [9], so that the results of the two different approaches can be compared.

In building the regression model for analyzing the data from the WHI RCT and OS, we will use the propensity score method. Compared with the piece-wise Cox model, the approach

we adopt here produces a smoother hazard ratio estimate and results in better model fit. The conclusions from [9] regarding the differing time-dependence of hazard ratio short-term vs. long-term are mostly found from the new analysis. Furthermore, the new results on average hazard ratio comparisons corroborate the findings from [9] that there is general agreement of the average hazard ratios between the RCT and OS components of WHI.

We organize the article as follows. In Section 2 the model is introduced. In Section 3 inference procedures on the hazard ratio and the average hazard ratio are established. In Section 4 results from simulation studies are presented and discussed. In Section 5, the proposed methods are applied to the WHI data. We conclude the article with a discussion section on related topics.

2. The short-term and long-term hazard ratio model

Let T be the survival time of interest, Z the indicator that the patient receives active treatment, and $\mathbf{W}$ the covariate vector of dimension p . Let $\mathbf{U} = (Z, \mathbf{W})'$, where “ $'$ ” indicates transpose of a vector. We postulate that the hazard function of T given $\mathbf{U}$ is

$$\lambda_{\mathbf{U}}(t) = \lambda_0(t) \frac{\exp(\boldsymbol{\alpha}'\mathbf{W})}{\exp(-\beta_1 Z)F_0(t) + \exp(-\beta_2 Z)(1 - F_0(t))}, \quad (1)$$

where β_1 and β_2 are scalar parameters, $\boldsymbol{\alpha}$ is a p -dimensional parameter, and $\lambda_0(t)$ is an unknown baseline hazard function with corresponding $F_0(t) = \exp(-\Lambda_0(t))$, where $\Lambda_0(t)$ is the cumulative hazard function.

Under this model, the hazard ratio of the treatment group over the control group at level $\mathbf{W} = \mathbf{w}$ is

$$\frac{\lambda_{Z=1, \mathbf{W}=\mathbf{w}}(t)}{\lambda_{Z=0, \mathbf{W}=\mathbf{w}}(t)} = \frac{1}{\exp(-\beta_1 Z)F_0(t) + \exp(-\beta_2 Z)(1 - F_0(t))}.$$

Similarly to the Cox proportional hazards model, the hazard ratio is independent of the covariate $\mathbf{W}$. However, the hazard ratio now in general is time-dependent, instead of being a constant as in the Cox proportional hazards model. The hazard ratio approaches the values $\exp(\beta_1)$ and $\exp(\beta_2)$ respectively as t tends to zero or the upper end of the support set of $F_0(t)$. Thus $\exp(\beta_1)$ and $\exp(\beta_2)$ can be interpreted as short-term and long-term hazard ratios respectively. When $\beta_1 = \beta_2$, this model reduces to the Cox proportional hazards model. Other patterns of the hazard ratio can also be realized, such as those corresponding to no initial effect, diminishing effect, crossing hazard or survival functions. Figure 1 shows various scenarios for the hazard ratio under model (1). Note that the model implies that the hazard ratio is monotone.

Let $R(t) = (1 - F_0(t))/F_0(t)$, the unknown baseline odds function. We will express model (1) as

$$\lambda_U(t) = \frac{\exp(\alpha' \mathbf{W})}{\exp(-\beta_1 Z) + \exp(-\beta_2 Z) R(t)} \frac{dR(t)}{dt}. \quad (2)$$

Note that $R(t)$ is an unknown non-decreasing baseline function with $R(0) = 0$. This re-expression of the model is for notional convenience and somewhat improved finite sample performance of the inference procedures to be developed later.

When there is substantial censoring, the parameters are still identifiable, though $\exp(\beta_2)$ may not have the long-term hazard ratio interpretation since there may be few or no data near the upper end of the support set of $R(t)$. Instead, β_2 is simply a parameter that modulates the change in the hazard ratio over the data range. Note that the hazard ratio is a semi-parametric function depending on both the parameter $\theta = (\beta_1, \beta_2, \alpha)'$ and the unknown function $R(t)$. This is different from the case with the usual Cox model extension for time-dependent hazard ratio, where an *ad hoc* function is typically used, resulting in a parametric form of the hazard ratio.

The two-sample version of model (2), without the covariate $\mathbf{W}$, was proposed by Yang and Prentice [18] in which a pseudo-likelihood approach was proposed to obtain estimators of θ and R , and the asymptotic properties of the estimators were studied for right-censored data. Yang and Prentice [19] established point-wise confidence intervals and simultaneous confidence bands for the hazard ratio and the average hazard ratio. Other related works include Tong, Zhu, and Sun [20] for current status data, and Garcia, Ma, and Yin [21] for efficiency improvement. Yang and Prentice [18] also briefly discussed two methods to extend the two-sample model to the regression setting, but didn't provide details on their asymptotic properties. The first method to extend the two-sample model gives model (2) here, where the short-term and long-term effects of Z are separated, but the effect of the covariate $\mathbf{W}$ remains constant. The second method is more general and separates short-term and long-term effects for all explanatory variables. In the notation here this method gives the model

$$\lambda_U(t) = \frac{1}{\exp(-\theta'_1 \mathbf{U}) + \exp(-\theta'_2 \mathbf{U}) R(t)} \frac{dR(t)}{dt}, \quad (3)$$

where θ_1, θ_2 are two $p+1$ dimensional parameter vectors. When all components of θ_2 are 0, this hazard function expression reduces to

$$\lambda_U(t) = \frac{1}{\exp(-\theta'_1 \mathbf{U}) + R(t)} \frac{dR(t)}{dt},$$

giving the conditional cumulative hazard function $\Lambda_U(t) = \log(1 + \exp(\theta'_1 \mathbf{U}) R(t))$. Thus the more general model (3) contains the proportional odds model as a sub-model when all components of θ_2 are 0. For model (3), Nieto-Barajas [22] provides a Bayesian analysis approach. For model (3) further extended to allow time-dependent covariates, Diao, Zeng

and Yang [23] studied the nonparametric maximum likelihood estimators (NPMLE) of the parameters.

Model (3) can be very useful in various settings, including serving as tool for checking model (1). Although model (2) is only a sub-model of (3), it may arguably be the most important one for our purposes. We will focus on model (2) in this article, but the proposed methods can be extended to model (3). There are several reasons for this focus: The dependence of the hazard ratio on the covariate under model (3) makes it more difficult to analyze, interpret or implement. If one uses the average of the hazard ratio function over all observed covariates, then different RCTs or OSs could have different results due to difference in covariate distributions, not in treatment effect. If one uses the hazard ratio function at a particular covariate level, it is not clear how representative it would be for comparison purpose that we pursue here. Also, in RCT and OS for a treatment in consideration, often the treatment is of the primary concern. The sample size is typically large for the different treatment groups, but not necessarily so for different groups of covariate characteristics, particularly if there are more than just a few covariates. Thus the resulting confidence intervals and bands from model (3) are likely to be wider and less informative. Furthermore, the number of parameters is almost doubled in model (3). Thus it is desirable to use the more parsimonious model (2), provided that it provides a good fit to the data.

3. The estimators and confidence intervals

Let C be the censoring variable, $X = \min(T, C)$ and $\delta = I(T < C)$ where $I(\cdot)$ is the indicator function. We assume that T and C are independent given U . The available data consist of the *i. i. d.* copies $(X_i, \delta_i, Z_i, W_i)$ of (X, δ, Z, W) , $i = 1, \dots, n$. We re-express model (1) as

$$\lambda_i(t) = \frac{1}{\gamma_1(\theta, U_i) + \gamma_2(\theta, U_i)R(t)} \frac{dR(t)}{dt}, \quad i=1, \dots, n, \quad (4)$$

where $\lambda_i(t)$ is the hazard function for T_i given U_i , $\gamma_j(\theta, U_i) = \exp(-\beta_j Z_i - \alpha W_i)$, $j = 1, 2$.

Let $h(t)$ be the hazard ratio of the treatment group over the control group. This function depends on the parameter θ and the baseline function $R(t)$. The NPMLE of the parameters can be used to obtain an estimator of $h(t)$. The resulting construction of confidence bands can be quite demanding computationally. We will have more discussion on this in Section 6. Here we develop a pseudo-likelihood estimator $\hat{\theta}$ of θ that is similar to that of [18] for the two-sample case. For $t = \max_i \{X_i\}$ and $\mathbf{b} \in \mathbb{R}^{p+2}$, the $p+2$ dimensional space of real numbers, define

$$\begin{aligned} \hat{P}(t; \mathbf{b}) &= \exp \left(- \int_{s \leq t} \frac{\sum_{i=1}^n \delta_i \gamma_2(\mathbf{b}, U_i) dI(X_i \leq s)}{\sum_{i=1}^n I(X_i \geq s)} \right), \\ \hat{R}(t; \mathbf{b}) &= \frac{1}{\hat{P}(t; \mathbf{b})} \int_{s \leq t} \frac{\hat{P}_-(s; \mathbf{b})}{\sum_{i=1}^n I(X_i \geq s)} \sum_{i=1}^n \delta_i \gamma_2(\mathbf{b}, U_i) dI(X_i \leq s), \end{aligned} \quad (5)$$

where $\hat{P}_-(s; \mathbf{b})$ denotes the left continuous version (in s) of $\hat{P}(s; \mathbf{b})$, and $\int_s f(s) d(X_i - s) = f(X_i)I(X_i - t)$ for any integrand f . For t beyond $\max_i \{X_i\}$, we extend the definitions of $\hat{P}(t; \mathbf{b})$

and $R(\hat{t}; \mathbf{b})$ by using their respective values at $\max_i \{X_i\}$. Note that we use the exponential form for $P(\hat{t}; \mathbf{b})$, rather than the product-limit form used in [18]. This is based on simulations and real data applications in which the exponential form indicates a more stable behavior.

Let $L(\boldsymbol{\theta}; R)$ be the likelihood function of $\boldsymbol{\theta}$ under model (2) when the function $R(t)$ is known, with the corresponding score vector $S(\boldsymbol{\theta}; R) = \partial L(\boldsymbol{\theta}; R) / \partial \boldsymbol{\theta}$. Define $Q(\mathbf{b}) = S(\mathbf{b}; R) |_{R(t)=R(\hat{t}; \mathbf{b})}$. Then the pseudo maximum likelihood estimator $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$ is the zero of $Q(\mathbf{b})$. Specifically, $\hat{\boldsymbol{\theta}}$ is the solution of the following system of equations in $\mathbf{b}$:

$$\begin{aligned} \sum_{i=1}^n \frac{Z_i [\delta_i \gamma_1(\mathbf{b}, U_i) - \hat{R}(\mathbf{X}_i; \mathbf{b})]}{\gamma_1(\mathbf{b}, U_i) + \gamma_2(\mathbf{b}, U_i) \hat{R}(\mathbf{X}_i; \mathbf{b})} &= 0, \\ \sum_{i=1}^n \left\{ \frac{Z_i \hat{R}(\mathbf{X}_i; \mathbf{b}) [\delta_i \gamma_2(\mathbf{b}, U_i) + 1]}{\gamma_1(\mathbf{b}, U_i) + \gamma_2(\mathbf{b}, U_i) \hat{R}(\mathbf{X}_i; \mathbf{b})} - \frac{Z_i}{\gamma_2(\mathbf{b}, U_i)} \ln \left(1 + \frac{\gamma_2(\mathbf{b}, U_i)}{\gamma_1(\mathbf{b}, U_i)} \hat{R}(\mathbf{X}_i; \mathbf{b}) \right) \right\} &= 0, \\ \sum_{i=1}^n \left\{ \delta_i \mathbf{W}_i - \frac{\mathbf{W}_i}{\gamma_2(\mathbf{b}, U_i)} \ln \left(1 + \frac{\gamma_2(\mathbf{b}, U_i)}{\gamma_1(\mathbf{b}, U_i)} \hat{R}(\mathbf{X}_i; \mathbf{b}) \right) \right\} &= 0. \end{aligned}$$

With the use of $R(\hat{t}; \mathbf{b})$, the estimating function $Q(\mathbf{b})$ does not involve the unknown function $R(t)$, so the finite dimensional parameter $\boldsymbol{\theta}$ can be estimated more easily. In data applications and simulation studies, a Quasi-Newton algorithm works well with a numerical approximation of the Jacobian matrix. More discussion on computational aspects will be given in Section 4. In Appendix A of the Supporting Web Materials we show that, under certain regularity conditions, the estimator for $\hat{\boldsymbol{\theta}}$ is strongly consistent and asymptotically normal.

Once $\hat{\boldsymbol{\theta}}$ is obtained, $R(t)$ can be estimated by $R(\hat{t}; \hat{\boldsymbol{\theta}})$. Thus under model (2), for the hazard ratio $h(t)$ we have the estimator

$$\hat{h}(t) = \frac{1 + \hat{R}(t; \hat{\boldsymbol{\theta}})}{\exp(-\hat{\beta}_1) + \exp(-\hat{\beta}_2) \hat{R}(t; \hat{\boldsymbol{\theta}})}.$$

To study its distributional properties, let

$$\boldsymbol{\Phi}_n(t) = \sqrt{n}(\hat{h}(t) - h(t)).$$

In Appendix B of the Supporting Web Materials, we show that under certain regularity conditions, the hazard ratio estimator is strongly consistent and $\boldsymbol{\Phi}_n(t)$ converges weakly to a zero-mean Gaussian process $\boldsymbol{\Phi}^*(t)$ with covariance process $\sigma_h(s, t)$ given there.

For a fixed t_0 in the data range, confidence intervals for $h(t_0)$ can be obtained from the asymptotic normality of $\hat{h}(t_0)$. To this end, an estimator of the asymptotic variance $\sigma_h(t_0, t_0)$ of $\hat{h}(t_0)$ is needed. A plug-in estimator can be obtained using $\hat{\boldsymbol{\theta}}$ and $R(\hat{t}; \hat{\boldsymbol{\theta}})$. For better small sample behavior, in Appendix B of the Supporting Web Materials, we use a Monte Carlo technique similar to that in [24] to obtain a variance estimator $\hat{\sigma}_h(t_0, t_0)$ for $\sigma_h(t_0, t_0)$. The basic idea is to approximate $\boldsymbol{\Phi}_n(t)$ by expressions involving integrals with respect to

$$M_i(t) = \delta_i I(X_i \leq t) - \int_{s \leq t} I(X_i \geq s) \frac{dR(s)}{\gamma_1(\boldsymbol{\theta}, \mathbf{U}_i) + \gamma_2(\boldsymbol{\theta}, \mathbf{U}_i) R(s; \boldsymbol{\theta})}, i=1, \dots, n,$$

and then obtain Monte Carlo approximation of the asymptotic distribution. With a logarithmic transformation, we have the asymptotic $100(1 - \alpha)\%$ confidence interval

$$\hat{h}(t_0) \exp \left(\mp z_{\alpha/2} \frac{\sqrt{\hat{\sigma}_h(t_0, t_0)}}{\sqrt{n} \hat{h}(t_0)} \right), \quad (6)$$

where $z_{\alpha/2}$ is the $100(1 - \alpha/2)\%$ percentile of the standard normal distribution.

To assess the overall treatment effect over time period $I = [a, b] \subset (0, \tau]$ where τ is the maximum follow-up time, as in [9] we consider the average hazard ratio on $(0, a]$:

$$\mu_a = \frac{1}{a} \int_{t \leq a} h(t) dt.$$

It can be estimated by $\hat{\mu}_a = \int_{t \leq a} \hat{h}(t) dt / a$. Weighted average hazard ratio $\int_{t \leq a} \hat{h}(t) w(t) dt$ can also be considered, where $w(t)$ is normalized to have $\int_{t \leq a} w(t) dt = 1$.

In Appendix B of the Supporting Web Materials, we show that $\hat{\mu}_a$ is strongly consistent and asymptotically normal, and that a consistent estimator $\hat{\sigma}_\mu^2(a)$ of the limiting variance $\sigma_\mu^2(a)$ can be obtained by a Monte Carlo method. With these results, an asymptotic $100(1 - \alpha)\%$ confidence interval for μ_a can be obtained as

$$\hat{\mu}_a \exp \left(\mp z_{\alpha/2} \frac{\hat{\sigma}_\mu(a)}{\sqrt{n} \hat{\mu}_a} \right). \quad (7)$$

We will look at these confidence intervals when comparing the overall treatment effects in WHI RCT and OS. More discussions on summary measures of treatment effect can be found in Section 6.

To assess the time-dependence of the treatment effect, a good visual inspection can be obtained from examining the confidence bands of $h(t)$ over a time interval $I = [a, b]$. To derive such confidence bands, we can work with $\max_{t \in I} |\Phi_n(t)/w_n(t)|$ for a properly chosen data-dependent weight function $w_n(t)$. In the literature for obtaining confidence bands, the weight function is often taken to be the square root of the limiting variance function, resulting in an equal-precision band whose bounds are proportional to the point-wise confidence intervals [24-25]. In Appendix C of the Supporting Web Materials, we will choose w_n to approximate $\sqrt{\hat{\sigma}_h(t, t)}$ by linearly interpolating estimators $\hat{\sigma}_h(t_i, t_i)$ at a few grid points t_i 's, and use it to construct approximate equal precision confidence bands for the hazard ratio via a Monte Carlo method.

4. Simulation studies

Various simulation studies and real data applications have been undertaken to investigate the behavior of the proposed estimators and confidence procedures. All numerical computations were done in MATLAB. To assess the efficiency of the pseudo-likelihood approach, we have compared the pseudo-likelihood estimators (PLE) to the NPMLE. Our experience indicates that the efficiency of the PLE is good for moderately sized samples and becomes very high as the sample size increases. Here we report the results from a representative study. For the results in Table 1 and Table 2, the lifetime variables were generated under model (2) with $R(t) = \exp(t) - 1$, yielding the standard exponential distribution for the control group when there was no covariate effect. The values of (β_1, β_2) were $(\log(0.9), \log(1.2))$ and $(\log(1.2), \log(0.8))$, representing a 1/3 increase or decrease over time from the initial hazard ratio, respectively, if there was no censoring. The covariate was a standard normal variable and the coefficient was 0.5. The censoring variable was the smaller of 3 and a log-normal distribution, where the normal distribution had mean c and standard deviation 0.5, with c chosen to achieve various censoring rates. The data were split into the treatment and control groups by a 1:1 ratio.

Table 1 reports the sample biases of the PLE for the average hazard ratio μ over $[0, 3]$ and for the model parameter $(\theta_1, \theta_2, \theta_3)$. For comparison, results for the NPMLE is also included. Let $t_1 < \dots < t_d$ be the uncensored untied observations. The NPMLE is obtained by maximizing the likelihood function $L(\theta, R(t))$ as a function of the parameter θ and the jumps of $R(t)$ at $t_1 < \dots < t_d$. Thus numerically it is a $d + p + 2$ -dimensional maximization problem. The computational burden can be reduced if we profile out $R(t)$ by maximizing $L(\theta, R(t))$ over $R(t)$ for fixed θ . For details see [23].

At $n = 100$, it can be seen both PLE and NPMLE had somewhat similar behaviors for the bias, except for μ at the 50% censoring rate, where larger biases occurred for the PLE. The biases were small for θ_1 and very small for θ_3 . For μ and θ_2 , the biases were more noticeable and increased with the censoring rate. As n increased to 400 and 800, the biases for θ_1 and θ_3 became very small and the biases for μ and θ_2 also greatly decreased. At the larger sample sizes, the biases for the two estimators were quite similar.

Table 2 reports the standard errors of the PLE and the NPMLE for the average hazard ratio μ and for the model parameter $(\theta_1, \theta_2, \theta_3)$. At $n = 100$, the two estimators had very similar standard errors, except for μ at the 50% censoring rate, where the standard errors for PLE were about 10% higher than that for the NPMLE. As n increased to 400 and to 800, the standard errors of the NPMLE and the PLE became very close to each other, even for μ at the 50% censoring rate.

The construction of confidence intervals for $h(t)$ and μ requires estimation of the limiting covariance function $\sigma_h(s, t)$ which involves the derivative $R(t; \theta)/\theta$ and the derivative matrix in $Q(\theta)/\theta$. Although analytic forms of these derivatives can be obtained, they are complicated and cumbersome. For simulation studies and real data applications, we approximate the derivatives by numerical derivatives with the jump size of 10^{-8} . Our experience suggests that the results are fairly stable with respect to the choice of the jump

size. To avoid the unstable behavior of estimators near the extremes of the data range, as in the literature we restrict the range of the confidence bands for $h(t)$. After the weight function w_n is obtained as described in Appendix C of the Supporting Web Materials, we consider the restricted time range $[\min \kappa, \max \kappa]$ where κ consists of data points at which $w_n(t)$ does not exceed the 95th percentile of $\{w_n(t_i): i = 1, \dots, m\}$, where t_i 's are the uncensored observations. Such restriction is necessary for yielding more meaningful results and avoiding extrapolation to regions where data are sparse, and often is not overly restrictive as illustrated by applications to the WHI data in the next section.

Our simulation studies suggest that the point-wise and simultaneous confidence intervals for $h(t)$ and the point-wise confidence intervals for μ have good coverage probabilities. Table 3 shows the results of a representative study. The same configuration as that in Table 1 and Table 2 was used to generate the data. In constructing the confidence band, the grid of the time points was $\{1, 1.5, 2, 2.5\}$. That is, the Monte Carlo estimators $\hat{\sigma}_h(t_i, t_i)$ were obtained for $t_i = 1, 1.5, 2, 2.5$ and used to get a weight function w_n by linear interpolation. This weight function w_n then was used in the confidence band construction as described in Appendix C of the Supporting Web Materials. The empirical coverage probabilities were obtained from 1000 repetitions, and for each repetition, the critical value $\hat{c}_a$ was calculated empirically from 2000 realizations of relevant conditional distributions. Note that with 1000 repetitions and $1.96 \sqrt{(.95)(.05)/1000} = 0.0135$ we expect the empirical coverage probabilities to be mostly greater than 0.9365. In Table 3, for h , the empirical coverage probabilities are greater than 0.9365 for all cases. With smaller sample sizes at $n = 100$ and $n = 200$, the confidence intervals and bands were somewhat conservative. As the sample size increased to $n = 400$, the empirical coverage probabilities got closer to the nominal level of 95%.

In Table 1 through Table 3, the covariates used in generating the data were standard normal variables, thus unbounded. In the proofs in the appendices, one assumption is that the covariates are bounded. We displayed the results here for unbounded covariates in order to see how robust the procedures are. When we restricted the covariates to be standard normal variables truncated at ± 3 , we obtained essentially the same results. They are omitted here to conserve space.

5. Applications to the WHI RCT and OS data

5.1. Propensity Score, Explained Randomness and the Choice of Covariates

In this section, we apply the methods developed in the previous sections to data from WHI estrogen plus progestin RCT and OS. As with Prentice et al. [9], we will look at the three outcomes of coronary heart disease (CHD), stroke, and venous thromboembolism (VTE). We will work with the subsets of 12,938 women in the RCT and 43,239 women in the OS who were with uterus at the time of WHI enrollment and for whom there are complete data for the three outcomes and for various baseline covariates. To reduce unnecessary missing data exclusions and collinearity among covariates, the following 17 baseline covariates are considered: age, body mass index (BMI) defined as weight in kilograms squared divided by height in meters, income, white race (no vs. yes), history of cardiovascular disease (yes vs. no), age at menopause, college degree (yes vs. no), school after high school (yes vs. no),

current smoker (yes vs. no), past smoker (yes vs. no), systolic blood pressure, daily servings of vegetables, daily servings of fruits, alcohol intake, treated diabetes (yes vs. no), exercise episodes per week, and physical functioning. To ensure a common interpretation of estrogen-plus-progestin hazard ratios in the RCT and the OS, we will use the same covariates in both the RCT and the OS. To compare the results on the treatment effect from WHI RCT and OS. We will use a propensity score approach. Theoretically the propensity score is not needed if a regression model is indeed correct with a specified set of independent variables. In applications the propensity score has often been used to balance the covariates in the treatment and control groups, toward reducing the bias in OS's in many fields [26-27]. The propensity score for an individual is defined as the conditional probability of being treated given the individual's covariates. Once estimated, the propensity score often can be used to reduce bias through matching, stratification, regression adjustment, or some combination of the three. In our applications here, although the sample sizes are very large, the effective sample sizes are quite small due to approximately 98% censoring. Thus matching and stratification may not be good options for the potential increase in variance due to a reduction in the effective sample size. As will be shown, the conventional way of using the propensity score in a regression model also leaves room for improvement.

For linear regression models, the coefficient of determination R^2 is a well-known measure of predictive ability of the model. Different interpretations of R^2 in the linear regression model have led to a large spectrum of R^2 -type measures in survival analysis [28-30]. Many of the proposed measures either are only defined for the Cox model, or are ineffective in the case of extra-heavy censoring. To assess the adequacy of the covariates selected for adjustment and to compare with the piece-wise Cox model, we use the measure of explained randomness [31] that is based on the Kullback-Leibler information gain. Let the conditional density of T given $\mathbf{U}$ be $f(t|\mathbf{u}, \boldsymbol{\theta})$, and

$$I(\xi) = E \{ \ln f(T|U, \xi) \} = \iint \ln f(t|u, \xi) f(t|u, \boldsymbol{\theta}) dt dH(u),$$

where H is the marginal distribution of $\mathbf{U}$. The explained randomness is

$$\rho^2 = 1 - \exp \{ -2I(\boldsymbol{\theta}) + 2I(0) \},$$

a measure that takes values in (0,1) with the interpretation of “proportion of the randomness” explained by the model. It can be estimated by

$$\hat{\rho}^2 = 1 - \exp \left\{ -\frac{2}{n} \sum_{i=1}^n \int \ln \frac{f(t|\mathbf{U}_i, \hat{\boldsymbol{\theta}})}{f(t|\mathbf{U}_i, 0)} f(t|\mathbf{U}_i, \hat{\boldsymbol{\theta}}) dt \right\}.$$

When there is substantial censoring, the estimated explained randomness can be very small. Often in the literature an *ad hoc* modification $\hat{\rho}_k^2$ is used, where $\hat{\rho}_k^2$ is defined similarly to $\hat{\rho}^2$ but with the denominator n replaced by k , the number of uncensored observations. A drawback of this modification is that the limit of $\hat{\rho}_k^2$ depends on the censoring distribution. To avoid this a different *ad hoc* adjustment can be made by replacing $f(t|u, \theta)dt$ with $I(t \leq \tau)f(t|u, \theta)dt / \int_x \tau f(x|u, \theta)dx$ in the definition of the explained randomness, with τ being the maximum follow-up time. For simplicity we will use $\hat{\rho}_k^2$.

If we combine the data from WHI RCT and OS to estimate the propensity score and use the propensity score as the sole covariate in model (1), then the estimated explained randomness is 0.85 and 0.84, for CHD OS and CHD RCT respectively. For regression adjustment with the propensity score in the literature, often the propensity score is used with a subset of the covariates on which it is based. Examination of the propensity score shows that age, BMI, income and white race are the most significant among the 17 variables. Let U consist of age, BMI, income, white race, and the propensity score. Then the estimated explained randomness is 0.86 and 0.90 for CHD OS and CHD RCT, respectively, indicating an improvement of the regression model with the added covariates.

Upon inspecting the propensity score, it can be seen that the coefficients of age and BMI have by far the most significant p -values. Thus, to account for the influence of covariates other than age and BMI more properly, we use U consisting of age, BMI, income, white race, and the propensity score resulting from the remaining the 15 covariates, excluding age and BMI. The resulting estimated explained randomness is 0.92 for CHD OS and 0.91 for CHD RCT. Instead of using the propensity score, if we choose U in model (1) to be the 15 variables that have significant coefficients in the propensity score, then the estimated explained randomness changes to 0.93 for CHD OS and 0.90 for CHD RCT, while the parameter dimension of the model increases from 7 to 17. Thus, to compare WHI RCT and OS, we will use model (1) with U obtained from this modified propensity score approach. Note that the propensity score is estimated using only the covariates and the treatment indicator, not the outcome variables. This is different from variable selection approaches that also use the outcome variables. The estimated explained randomness is given for various selections of U in Table 4. It shows that the modified propensity score approach improves the model fit.

5.2. The Hazard Ratios and the Ratio of Average Hazard Ratios

For CHD, VTE, and stroke, we first compare the hazard ratio in the RCT and the OS components of the WHI via the point-wise confidence intervals and confidence bands. The intervals and bands presented here are based on the Monte Carlo method with 5,000 realizations of relevant conditional distributions. For the RCT, the time from initiation of the current episode for the estrogen-plus-progestin was defined as the time since randomization, and for the OS, it was defined as the time since observational study enrollment. In constructing the confidence band, we used the grid of the time points $\{.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8\}$. For each of the three outcomes, we used the same scale in the plots for both RCT and OS. This lead to portions of the plots truncated for the RCT results.

For CHD, the 95% confidence intervals and confidence bands are given in Figure 2 (a) and (b), for the RCT and the OS respectively. For the CHD RCT, there is a decreasing trend over time and evidence that the hazard ratio is more than 1 during the early time period. These results agree with those in [9], where the piece-wise Cox model was used partitioning the time axis with cut-off points at 2 and 5 years. For the CHD OS, the hazard ratio is nearly constant over time, which differs from the hazard ratios in [9]. This may be in a large part due to the modeling differences in the approaches. For the estrogen plus progestin group in WHI OS, let B be the time a woman had used estrogen plus progestin at baseline, which was determined by going back in time from the OS enrollment until a gap of 1 year or longer in estrogen-plus-progestin usage was encountered. Define B to be zero for the control group of WHI OS and for both arms of WHI RCT. The piece-wise Cox model used in [9] is that given (U, B) , the hazard function is

$$\lambda_{U,B}(t) = \lambda_0(t) \exp(\alpha' \mathbf{W}) \exp(\beta_1 Z_1(t) + \beta_2 Z_2(t) + \beta_3 Z_3(t)), \quad (8)$$

where $\lambda_0(t)$ is an unknown baseline hazard function, $Z_1(t) = ZI(t + B \in [0, 2))I(t > 0)$, $Z_2(t) = ZI(t + B \in [2, 5))I(t > 0)$, and $Z_3(t) = ZI(t + B \geq 5)I(t > 0)$. This model has parameters pertaining to the change of hazard ratio function over time in the $t+B$ scale. In comparison, the model

$$\lambda_U(t) = \lambda_0(t) \exp(\alpha' \mathbf{W}) \exp(\beta_1 ZI(t \in [0, 2)) + \beta_2 ZI(t \in [2, 5)) + \beta_3 ZI(t \geq 5)) \quad (9)$$

has parameters pertaining to the change of hazard ratio function over time in the t scale or study time scale. It is possible to consider the model

$$\lambda_{U,B}(t) = \lambda_0(t) \frac{\exp(\alpha' \mathbf{W})}{\exp(-\beta_1 Z) F_0(t+B) + \exp(-\beta_2 Z) (1 - F_0(t+B))}. \quad (10)$$

The relationship between model (10) and model (1) is similar to the relationship between model (8) and model (9). Because both t and $t + B$ appear in model (10), it is more difficult to develop and implement a pseudo likelihood approach, as there is no closed form parallel to the estimated $R(t)$ function in equation (5). An NPMLE approach seems possible. Another option may be some iterative procedure with Breslow-type estimator of $R(t)$. These considerations will be explored separately. For $B \equiv 0$ as for the case of WHI RCT data, model (10) coincides with model (2). This helps explain the good agreement of the CHD RCT results here with those in [9], and the difference between the CHD OS results here with those in [9]. For CHD OS, neither the confidence results here nor those in [9] indicate a hazard ratio as a function of time since OS enrollment that is clearly < 1 or > 1 for any portion of the data range.

For VTE, the 95% confidence intervals and confidence bands are given in Figure 2 (c) and (d), for RCT and OS respectively. For both RCT and OS, there is a decreasing trend over time, and there is indication that the hazard ratio is more than 1 early on. These results agree with those in [9].

For stroke, the 95% confidence intervals and confidence bands are given in Figure 2 (e), (f), for RCT and OS respectively. Note that under model (1), the hazard ratio is monotone, whereas in the piece-wise Cox model approach used in [9] the hazard ratio could be U-shaped or upside-down U-shaped. From [9], the hazard ratio is monotone with CHD and VTE for RCT and OS, which may explain a general good agreement between the results here and those in [9]. In the case for stroke, Prentice et al. [9] noted that there were remaining sources of discrepancy between the RCT and OS results. For the RCT data with stroke, without covariate adjustment, Yang [32] showed that the piece-wise Cox model approach gives a U-shaped hazard ratio for the partition with 3 and 6 years, and an upside-down U-shaped hazard ratio for the partition with 2 and 5 years. In terms of the failure probability difference, these two different partitions were shown to result in better agreement with the Kaplan-Meier estimators in different parts of the data range. The short-term and long-term hazard ratio model provided a good compromise between the two different partitioning approaches. For the covariate-adjusted analysis here, we can compare model fit via the estimated explained randomness. For the RCT data with stroke, when the piece-wise Cox model (9) was fit, the resulting estimated explained randomness is 0.87 for the partitioning with 2 and 5 years, and 0.91 for the partitioning with 3 and 6 years. For the OS data, the estimated explained randomness is 0.92 for both partitions. The model approach we use here results in the estimated explained randomness of 0.92 and 0.93 for RCT and OS respectively. Thus the explained randomness indicates that the partition with 3 and 6 years may fit better than the partition with 2 and 5 years in the piece-wise Cox model approach, and that the modeling approach here may provide a better fit than both partitions without having to consider which partition to work with.

Note that for cases (a), (c), (d) and (e), the confidence bands and point-wise confidence intervals become wider for small t and for large t . For the cases (b) and (f), the sparsity of data early on is more pronounced as shown in Table 5 of [9]. The dominating influence of data at later times possibly contributes to the flatness of confidence bands and intervals, as the function $R(t)$ in the model is estimated using all data.

Although the improvement in the explained randomness outlined above gives some tangential evidence that model (2) with the chosen regression model is reasonable, checking goodness of fit of the model is an important part of model building. One main interest on model (2) is to see whether the covariate effect is indeed proportional. We will formally explore relevant tests elsewhere and use some simple graphic displays here to see if model (2) is reasonable. Let $\hat{\alpha}$ be the estimated covariate coefficient vector and divide the sample into two groups by the median of the observed score $\hat{\alpha}'\mathbf{W}$. Under model (1), the plots of the log cumulative hazard functions should be approximately parallel. Figure 3 shows that it is indeed the case for CHD RCT and CHD OS. The plots for other cases are similar and are omitted here.

Next we look at the average hazard ratio. Since the maximum follow-up time is 8.4 years for WHI RCT and 8.6 years for WHI OS, we will use the time period 0-8.4 years to calculate the average hazard ratios. To compare the average hazard ratios between RCT and OS, we consider the ratio of the average hazard ratio for the OS over that for the RCT. The estimates and the 95% confidence intervals are given in Table 5, where the results from [9] are also

included. From Table 5, we see that, there is general good agreement between the results from [9] and the results from using the short-term and long-term hazard ratio model, more so for CHD, the primary outcome of the WHI RCT. The proposed method and [9] both indicate that after the covariate adjustment, the average hazard ratios for the RCT and OS are much closer to each other, and that for none of the three outcomes is the ratio of the average hazard ratios significantly different from 1.

6. Discussion

The short-term and long-term hazard ratio model with covariate adjustment may be useful in a wide range of applications. It includes the case of proportional hazards and allows various time-dependent patterns for the hazard ratio. For displaying the time-dependent pattern, we have constructed point-wise confidence intervals and confidence bands. For assessing the overall treatment effect, we have obtained an estimator and the corresponding confidence intervals for the average hazard ratio, defined as a function of time from WHI enrollment. In applications to the WHI RCT and OS data, we reduced the number of explanatory variables via a modified propensity score approach to balance between reducing bias and keeping the variance in check. Compared with the Cox model or the piece-wise Cox model, this approach eliminates the need to consider whether and how the time axis should be partitioned, and results in better model fit in terms of explained randomness.

An important feature of model (2) is that the covariate effect is proportional, leading to a more parsimonious model than model (3). It could be a strong assumption, and severe bias in the treatment effect estimate could result if the assumption is violated. It would be very helpful to examine the consequences of mis-specifying the covariate effect as proportional, and to formally check the model fitness. Yang and Zhao [33] proposed two omnibus tests for checking the two-sample case of model (2). It is possible to extend one of the tests, based on the martingale residuals, to model (2). Alternatively, one can use the NPMLE in deriving the test, similarly to Chen, Lin and Zeng [34] for the linear transformation models.

In this article we have focused on the hazard ratio and average hazard ratio to describe and summarize, respectively, the treatment effect that is possibly time-dependent. In the literature other measures have also been proposed. For example, the survival probability could be considered, at a late time point t' where it can still be reliably estimated. Also, the restricted mean survival time over the time period $[0, t']$ could be used.

Our approach appears to have high semiparametric efficiency for large samples. It is worthwhile to also consider an NPMLE based approach. Simulations show that using the PLE proposed here as the initial value can much speed up the computation of the NPMLE. For constructing the confidence bands, it is possible to use a resampling method that is similar to that used in Chen et al. [34] for checking the linear transformation model. Let $r = d + p + 2$, the dimension of unknown parameters in the NPMLE approach. Then the resampling method requires the $r \times r$ inverse Hessian matrix and the r dimensional score vector evaluated at each observation. Our initial exploration indicates that for large r this approach gives results very close to what we obtained here, but takes substantially more computing time. Using MATLAB from the High-Performance Computing Helix Systems at

the NIH, for r around 500 and with 2000 resampling repetitions, the PLE based confidence band typically takes less than 1 second, while the NPMLE based confidence band takes about 5 hours. For r around 1000 and with 2000 resampling repetitions, the PLE based confidence band typically takes about 6 seconds, while the NPMLE based confidence band would take more than 50 hours. Together with our collaborators, we plan to examine the NPMLE approach thoroughly with attention to speed up the computation, and report the results in the future.

To make inference on the hazard ratio function, it is also possible to use the nonparametric approach. Gilbert et al. [35] constructed point-wise confidence intervals and simultaneous confidence bands of the hazard ratio without covariate adjustment. The nonparametric approach offers more modeling flexibility. The resulting confidence intervals and confidence bands tend to be substantially wider, particularly at the extremes of the data range where data may be sparse, as illustrated for the CHD RCT in [19].

Although we have focused on model (2), the asymptotic analysis can be extended with more tedious notation and algebra to more elaborate versions, and to model (3). For example, if we hypothesize that the covariate effect is the same for WHI RCT and OS, and that the hazard ratio in the OS is a constant multiple of the hazard ratio in the RCT, then we can pool the WHI RCT and OS data and fit the model

$$\lambda_U(t) = \frac{\exp(\alpha' \mathbf{W} + vS + \xi ZS)}{\exp(-\beta_1 Z) + \exp(-\beta_2 Z)R(t)} \frac{dR(t)}{dt},$$

where S is the indicator that the patient is in the OS and e^{ξ} represents the ratio of the hazard ratio from the OS over that from the RCT. Note that under this model, the hazard ratios in the OS and the RCT are proportional to each other and continue to be free of the covariate $\mathbf{W}$, although each can be time-dependent. This is a strong assumption, and results in lower estimated explained randomness than that of the approach in Section 5. To relax the assumption of proportional hazard ratios, we can also consider the model

$$\lambda_U(t) = \frac{\exp(\alpha' \mathbf{W} + vS)}{\exp(-\beta_1 Z - \xi_1 ZS) + \exp(-\beta_2 Z - \xi_2 ZS)R(t)} \frac{dR(t)}{dt}.$$

Under this model, the hazard ratios from RCT and OS are given by

$$\frac{1+R(t)}{\exp(-\beta_1) + \exp(-\beta_2)R(t)}, \frac{1+R(t)}{\exp(-\beta_1 - \xi_1) + \exp(-\beta_2 - \xi_2)R(t)},$$

respectively. This model has three more parameters than in Section 5, and the ratio of average hazard ratios is much more complicated.

The explained randomness is one of few measures that can be used on different models, but there are no formal tests on whether one model is better than another, or which explanatory variables can be eliminated. More research may be needed. If the focus is not on comparison of different models but rather on the selection of covariates, then techniques from the wealth of current variable selection literature can be used and adapted for models (2) and (3). This diverse range of topics are worthy of further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Various patterns of the hazard ratio under model (1), when the baseline distribution (with θ being a zero vector) is the standard exponential.

(a)

(b)

(c)

(d)

Figure 2.

95% point-wise confidence intervals and confidence bands of the hazard hazard for the WHI data: Outside solid lines—95% Confidence band; Outside dash-dotted lines—95% point-wise confidence intervals; Central dashed line—the estimated hazard ratio. (a) CHD CT; (b) CHD OS; (c) VTE CT; (d) VTE OS; (e) Stroke CT; (f) Stroke OS.

Figure 3.

Log cumulative hazard functions for the two groups formed by the observed median of the score $\hat{\alpha}W$ for the WHI CHD data: (a) CHD RCT; (b) CHD OS. Solid line—lower half; Dashed line—upper half.

Table 1

Biases of the pseudo-likelihood estimators (PLE) and the nonparametric maximum likelihood estimators (MLE) for the average hazard ratio (μ) and the model parameters ($\theta_1, \theta_2, \theta_3$) under model (2), based on 1000 repetitions: (a) $n = 100$; (b) $n = 400$; (c) $n = 800$. The true value of $(\mu, \theta_1, \theta_2, \theta_3)$ is (1.092, -.105, 0.182, 0.406) for the .9 $\uparrow$ 1.2 case and (0.904, 0.182, -0.223, 0.406) for the 1.2 $\uparrow$.8 case respectively.

(a) $n = 100$							
Parameter	Method	Hazard ratio					
		.9 $\uparrow$ 1.2 Censoring			1.2 $\downarrow$.8 Censoring		
		10%	30%	50%	10%	30%	50%
μ	PLE	0.1064	0.1862	0.2473	0.0780	0.1610	0.2621
	MLE	0.0992	0.1655	0.2067	0.0748	0.1520	0.2288
θ_1	PLE	-0.0615	-0.0362	0.0145	-0.0751	-0.0705	-0.0313
	MLE	-0.0674	-0.0527	-0.0115	-0.0771	-0.0768	-0.0540
θ_2	PLE	0.1776	0.2679	0.3678	0.1411	0.2659	0.4427
	MLE	0.1776	0.2669	0.3651	0.1406	0.2656	0.4406
θ_3	PLE	0.0191	0.0063	-0.0135	0.0196	0.0132	0.0111
	MLE	0.0211	0.0134	0.0007	0.0203	0.0152	0.0112
(b) $n = 400$							
Parameter	Method	Hazard ratio					
		.9 $\uparrow$ 1.2 Censoring			1.2 $\downarrow$.8 Censoring		
		10%	30%	50%	10%	30%	50%
μ	PLE	0.0315	0.0781	0.1357	0.0164	0.0467	0.0980
	MLE	0.0308	0.0769	0.1257	0.0168	0.0473	0.0973
θ_1	PLE	-0.0213	-0.0288	-0.0199	-0.0203	-0.0309	-0.0305
	MLE	-0.0213	-0.0288	-0.0230	-0.0203	-0.0309	-0.0305
θ_2	PLE	0.0516	0.1239	0.2078	0.0275	0.0774	0.1698
	MLE	0.0516	0.1239	0.2077	0.0275	0.0774	0.1698
θ_3	PLE	0.0019	0.0021	-0.0034	0.0019	0.0025	0.0027
	MLE	0.0019	0.0021	-0.0015	0.0018	0.0025	0.0026
(c) $n = 800$							
Parameter	Method	Hazard ratio					
		.9 $\uparrow$ 1.2 Censoring			1.2 $\downarrow$.8 Censoring		
		10%	30%	50%	10%	30%	50%
μ	PLE	0.0167	0.0364	0.0960	0.0097	0.0183	0.0586
	MLE	0.0165	0.0358	0.0920	0.0100	0.0187	0.0591
θ_1	PLE	-0.0122	-0.0138	-0.0156	-0.0115	-0.0125	-0.0165
	MLE	-0.0121	-0.0138	-0.0158	-0.0115	-0.0124	-0.0165
θ_2	PLE	0.0270	0.0549	0.1474	0.0167	0.0300	0.0880
	MLE	0.0270	0.0549	0.1474	0.0168	0.0300	0.0880
θ_3	PLE	-0.0010	0.0004	-0.0014	-0.0008	0.0001	-0.0017

		(c) $n = 800$					
Parameter	Method	Hazard ratio					
		.9 ↑ 1.2 Censoring			1.2 ↓ .8 Censoring		
		10%	30%	50%	10%	30%	50%
	MLE	-0.0010	0.0004	-0.0009	-0.0008	0.0001	-0.0017

Table 2

Standard errors of the pseudo-likelihood estimators (PLE) and the nonparametric maximum likelihood estimators (MLE) for the average hazard ratio (μ) and the model parameters ($\theta_1, \theta_2, \theta_3$) under model (2), based on 1000 repetitions: (a) $n = 100$; (b) $n = 400$; (c) $n = 800$. The true value of ($\mu, \theta_1, \theta_2, \theta_3$) is (1.092, -.105, 0.182, 0.406) for the .9 $\uparrow$ 1.2 case and (0.904, 0.182, -0.223, 0.406) for the 1.2 $\uparrow$.8 case respectively.

(a) $n = 100$							
Parameter	Method	Hazard ratio					
		.9 $\uparrow$ 1.2 Censoring			1.2 $\downarrow$.8 Censoring		
		10%	30%	50%	10%	30%	50%
μ	PLE	0.3615	0.4739	0.5431	0.3088	0.4421	0.5763
	MLE	0.3505	0.4439	0.4934	0.2957	0.4173	0.5175
θ_1	PLE	0.4263	0.4276	0.4450	0.4777	0.4854	0.4971
	MLE	0.4325	0.4338	0.4472	0.4783	0.4842	0.4995
θ_2	PLE	0.6038	0.7432	0.9002	0.5401	0.7252	0.9456
	MLE	0.6038	0.7429	0.9009	0.5424	0.7251	0.9463
θ_3	PLE	0.2219	0.2527	0.2931	0.2249	0.2549	0.3001
	MLE	0.2220	0.2527	0.2947	0.2246	0.2532	0.2940
(b) $n = 400$							
Parameter	Method	Hazard ratio					
		.9 $\uparrow$ 1.2 Censoring			1.2 $\downarrow$.8 Censoring		
		10%	30%	50%	10%	30%	50%
μ	PLE	0.1787	0.2656	0.3727	0.1280	0.1911	0.3198
	MLE	0.1781	0.2648	0.3580	0.1278	0.1904	0.3129
θ_1	PLE	0.2083	0.2195	0.2355	0.2234	0.2407	0.2679
	MLE	0.2081	0.2196	0.2395	0.2234	0.2407	0.2677
θ_2	PLE	0.3048	0.4478	0.6344	0.2261	0.3348	0.5583
	MLE	0.3048	0.4477	0.6343	0.2261	0.3348	0.5583
θ_3	PLE	0.1104	0.1225	0.1476	0.1113	0.1231	0.1454
	MLE	0.1104	0.1225	0.1463	0.1113	0.1231	0.1452
(c) $n = 800$							
Parameter	Method	Hazard ratio					
		.9 $\uparrow$ 1.2 Censoring			1.2 $\downarrow$.8 Censoring		
		10%	30%	50%	10%	30%	50%
μ	PLE	0.1221	0.1814	0.3058	0.0888	0.1192	0.2222
	MLE	0.1218	0.1808	0.3003	0.0887	0.1190	0.2192
θ_1	PLE	0.1501	0.1639	0.1803	0.1624	0.1748	0.1946
	MLE	0.1501	0.1639	0.1807	0.1624	0.1748	0.1945
θ_2	PLE	0.2081	0.3067	0.5130	0.1606	0.2159	0.3783
	MLE	0.2081	0.3067	0.5129	0.1605	0.2159	0.3783
θ_3	PLE	0.0749	0.0826	0.0979	0.0754	0.0828	0.0982

		(c) $n = 800$					
Parameter	Method	Hazard ratio					
		.9 ↑ 1.2 Censoring			1.2 ↓ .8 Censoring		
		10%	30%	50%	10%	30%	50%
	MLE	0.0749	0.0826	0.0978	0.0754	0.0829	0.0982

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Table 3

Empirical coverage probabilities of the 95% confidence band of the hazard ratio (CB), the 95% confidence interval of the hazard ratio at fixed point $t = 1$ ($h(1)$), and the 95% confidence interval of the average hazard ratio (μ) under model (2), based on 1000 repetitions.

Hazard ratio	Censoring	n	CB	$h(1)$	μ
.9 ↑ 1.2	10%	100	0.969	0.973	0.971
	30%		0.967	0.971	0.968
	50%		0.963	0.972	0.966
	10%	200	0.962	0.972	0.959
	30%		0.952	0.964	0.962
	50%		0.967	0.969	0.973
	10%	400	0.952	0.954	0.965
	30%		0.944	0.954	0.957
	50%		0.953	0.954	0.961
	10%	100	0.952	0.959	0.970
1.2 ↑ .8	30%		0.972	0.978	0.977
	50%		0.973	0.967	0.976
	10%	200	0.965	0.967	0.966
	30%		0.962	0.967	0.962
	50%		0.960	0.952	0.967
	10%	400	0.952	0.955	0.959
	30%		0.959	0.949	0.963
	50%		0.949	0.956	0.967

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Table 4

Estimated explained randomness for various models: Model I – the propensity score as the only covariate; Model II – with covariates age, BMI, income, white race, and the propensity score; Proposed – with covariates age, BMI, income, white race, and the modified propensity score.

	CHD		VTE		Stroke	
	OS	RCT	OS	RCT	OS	RCT
Model I	0.85	0.84	0.75	0.89	0.83	0.87
Model II	0.86	0.90	0.82	0.91	0.88	0.89
Proposed	0.92	0.91	0.84	0.91	0.93	0.92

Table 5

Ratio of the average hazard ratio in the OS over that in RCT for the WHI data, from the proposed method and from Prentice et al. (2005) (95% confidence intervals in parentheses).

	Proposed	Prentice et al. (2005)
CHD	.85(.59, 1.26)	.93(.64, 1.36)
VTE	.70(.47, 1.04)	.84(.54, 1.28)
Stroke	.82(.55, 1.25)	.76(.49, 1.18)