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Methods for Estimating Center Effects on Recurrent Events

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Abstract

In this article, we develop methods for quantifying center effects with respect to recurrent event data. In the models of interest, center effects are assumed to act multiplicatively on the recurrent event rate function. When the number of centers is large, traditional estimation methods that treat centers as categorical variables have many parameters and are sometimes not feasible to implement, especially with large numbers of distinct recurrent event times. We propose a new estimation method for center effects which avoids including indicator variables for centers. We then show that center effects can be consistently estimated by the center-specific ratio of observed to expected cumulative numbers of events. We also consider the case where the recurrent event sequence can be stopped permanently by a terminating event. Large sample results are developed for the proposed estimators. We assess the finite-sample properties of the proposed estimators through simulation studies. The method is then applied to national hospital admissions data for end stage renal disease patients.

Keywords

Center effects; Proportional rates model; Recurrent event data; Terminating event

1 Introduction

Large registry databases are often used to compare outcomes across centers. Comparisons of each center's outcomes relative to the population average assist in understanding the influence of facility on patient prognosis. Such evaluations may lead, in the short term, to the identification of centers with significantly better or worse than average outcomes and, ultimately, to an improvement in the quality of patient care. For example, dialysis facility-specific measures of hospitalization rates may reflect a facility's quality of service relative to a national norm or population level. Published reports of such facility-specific evaluations may assist end-stage renal disease patients about to initiate dialysis in selecting a health care provider. Statistical models for multi-center studies have been developed for various outcomes, including clustered continuous, binary and time-to-failure data (e.g. Gould 1998; Agresti and Hartzel 2000; Localio, Berlin, Ten Have, and Kimmel 2001; Glidden and Vittinghoff 2004).

Existing methods for estimating center effects can be classified as fixed effects or random effects models. In the fixed effect approach, center effects are treated as fixed and have a direct interpretation (e.g., each center is compared to a pre-specified reference level). On the other hand, random effect models typically treat the center effects as random variates following a specific distribution across centers, with only one additional parameter indexing the variance of the random effects. Conclusions regarding a given center effect will be influenced by the whole population from which this particular center is randomly selected. The estimation procedure depends on the distribution assumed for the random effects, and the likelihood typically does not have a closed form unless the random effect distribution is carefully chosen. Although each method has its advantages and disadvantages, we emphasize fixed effects models in this report, owing in part to the motivating example, which we now describe.

The problem motivating this research arose in a nationwide dialysis facility assessment study on patient morbidity. Frequency of hospitalization is an important factor to be considered when attempting to address issues of escalating medical costs. As a measure of hospitalization, admission to the hospital can be viewed as a recurrent event since dialysis patients may have multiple hospital admissions after the initiation of end-stage renal disease (ESRD) therapy. Each year, over 5,000 dialysis facilities are assessed in the U.S., with facility sizes ranging from fewer than 10 to more than 500 dialysis patients. Each facility's hospitalization experience is then evaluated by comparing its outcomes to a risk adjusted national average.

Several models have been developed for inference on the marginal mean or rate function for a recurrent event. The proportional rates model of Lin, Wei, Yang, and Ying (2000) is widely used for the analysis of recurrent event data, due to flexibility and its ease of implementation. This method assumes that subjects are independent units. To account for within cluster correlation, Schaubel and Cai (2005b) proposed two semiparametric proportional rates models for clustered recurrent event data with 1) common baseline rates and 2) cluster specific baseline rates. When the estimation of center effects for recurrent event data is of interest, one might consider multiplicative center effects in the common baseline rates model of Schaubel and Cai (2005b). We will discuss this model in detail in the next section. Due to the large number of facilities in the motivating example, traditional estimation methods that treat centers as categorical variables have many parameters and are sometimes not feasible to implement, especially when the number of distinct recurrent event times is large. In order to circumvent this problem, we develop a new estimation method using fixed effects models for recurrent event data. The proposed method is based on the ratio of the observed to expected number of recurrent events, and can be generalized to accommodate a setting wherein a terminal event (e.g., death) is also present.

In this paper, we specify the fixed center effect models (Section 2); describe the estimation method (Section 3); derive pertinent theoretical properties of the proposed methods (Section 4); assess the performance of the proposed estimators and compare them with those obtained from the traditional estimation method (Section 5); apply the proposed method to the motivating example (Section 6); and conclude the paper with some discussion (Section 7).

2 Center effect Models

Let $N^*(t)$ denote the number of events that occur over interval $(0, t]$. Let $\mathbf{Z}(t)$ be a p -vector of external covariates (Kalbfleisch and Prentice 2002). Let $k = 1, \dots, K$ index center, with centers assumed to be independent of each other. Center size is given by n_k , with $\sum_{k=1}^K n_k$ being the total sample size. Let G be the center index. Assuming a multiplicative center effect on the rates of the counting process $N^*(t)$, an appropriate proportional rates model can be specified as

$$E \{dN^*(t) | G=k, \mathbf{Z}(t)\} = \exp \left\{ \beta_0^{*T} \mathbf{Z}(t) \right\} \theta_k^* d\mu_0^*(t), \quad (1)$$

where β_0^* is an unknown p -vector of regression parameters, $\mu_0^*(t)$ is an unspecified baseline cumulative rate function, and θ_k^* represents the (fixed) center effect for the k -th center, $k = 1, \dots, K$. The θ_k^* are positive valued parameters. For identifiability and interpretability, we introduce the constraint $\sum_{k=1}^K w_k \theta_k^* = 1$, for some pre-specified positive weights w_k , $k = 1, \dots, K$ where $\sum w_k = 1$. Thus, θ_k^* can be interpreted as the center effect relative to this weighted average. Although more complicated weighting may be possible, the weight functions we suggest are fixed and known at time $t = 0$, and typically are taken to be $w_k = 1/K$ or $w_k = n_k/n$. The asymptotic properties we derive in Section 4 treat the weight function as known.

When a terminal event (e.g., death) is present, a subject's recurrent event sequence stops at the time of the terminal event, which we denote by D . We consider a partial-marginal model (e.g. Cook and Lawless 1997; Schaubel and Cai 2005a; Ye, Kalbfleisch, and Schaubel 2007) which specifies the marginal occurrence rates for subject in the k th center conditional on being alive as

$$E \{dN^*(t) | G=k, \mathbf{Z}(t), D \geq t\} = \exp \left\{ \beta_0^{*T} \mathbf{Z}(t) \right\} \theta_k^* d\mu_0(t). \quad (2)$$

Analogous to model (1), fixed center effects are assumed. A constraint on the θ_k 's, such as $\sum_{k=1}^K w_k \theta_k = 1$ with known weight terms w_k , is again necessary for the identifiability of $\mu_0(t)$.

One may notice that by letting $D \rightarrow \infty$, model (2) reduces to model (1). Thus, we emphasize model (2) henceforth with estimation and inference under model (1) being similar to that under model (2).

An alternative form to (2) which incorporates center effects within the exponential function is given by

$$E \{dN^*(t) | G=k, \mathbf{Z}(t), D \geq t\} = \exp \left\{ \eta_k + \beta_0^{*T} \mathbf{Z}(t) \right\} d\mu_0(t), \quad (3)$$

where η_k represents the center effects, with $\exp(\eta_k) = \theta_k$. Model (3) is equivalent to model (2), but this form is used more frequently due to the fact that $\{\eta_1, \dots, \eta_K\}$ and β_0 in model (3) can be estimated simultaneously through standard applications of well-known statistical

software for the Cox model (e.g., *PHREG*, *coxph*) which may be convenient in some settings. However, a drawback to Model (3) for databases with a large number of centers is the resulting dimension of the design matrix, which may render estimation prohibitive. For example, with respect to the setting which motivated this report, there are approximately $K = 5,363$ dialysis facilities in the United States. In addition, estimates of η_k 's can be $-\infty$, which plays havoc with the standardization.

Motivated by such considerations, we propose (Section 3) a new estimator for center effects θ_k under model (2) without increasing the dimension of the design matrix as the number of centers increases. We also derive an alternative estimator, based on a transformation of $\eta = \{\eta_1, \dots, \eta_K\}$ from Model (3), which has the same limiting value (i.e., is relative to the same reference) as $\hat{\theta}_k$ based on model(2).

In the following, we specify the independent left truncation and right censoring assumption. In many applications, subjects may enter the study at different stages of follow-up and be followed for a limited time. Thus, $N^*(t)$ may not be fully observed before D . Let B and C denote the left truncation and right censoring time respectively. Define the at risk process $Y(t) = I(B < t \leq C \wedge D)$ with $a \wedge b = \min(a, b)$. The observed cumulative number of events as of time t is $N(t) = \int_0^t Y(s) dN^*(s)$. Under the assumption that $N^*(t)$ is subject to independent left truncation and right censoring, which can be specified as

$$E\{dN^*(t) | G=k, \mathbf{Z}(t), Y(t)=1\} = E\{dN^*(t) | G=k, \mathbf{Z}(t), D \geq t\},$$

we have that

$$E\{dN(t) | G=k, \mathbf{Z}(t), Y(t)\} = Y(t) \exp\left\{\beta_0^T \mathbf{Z}(t)\right\} \theta_k d\mu_0(t). \quad (4)$$

3 Estimation Methods

In this section, we first propose a new estimation method for center effects θ_k under model (2) that is based on the ratio of the observed to expected number of recurrent events. Second, we propose an alternative estimator for θ_k based on the more commonly used Model (3). The role of the second estimator, which is semiparametrically efficient, is mostly to serve as a comparison to the first estimator.

We note that model (2) is actually a special case of a cluster-specific proportional rates model with $d\mu_{0k}(t) = \theta_k d\mu_0(t)$. Schaubel and Cai (2005b) studied the cluster-specific proportional rates model for recurrent event data. With the estimators for β and $\mu_{0k}(t)$ as in Schaubel and Cai (2005b), we obtain an estimator for $\mu_0(t)$ subject to the constraint on θ_k specified in Section 2. An estimator of θ_k follows by replacing the true values with the corresponding estimators for β and $\mu_{0k}(t)$ in the expected number of recurrent events for center k .

We begin by defining the following relevant notation. For subject i ($i = 1, \dots, n$), let $N_i(t)$, $Y_i(t)$, $\mathbf{Z}_i(t)$, G_i , B_i and C_i be as defined above. Let $G_{ik} = I(G_i = k)$, where $I(\cdot)$ is an indicator

function. In addition, let $Y_{ik}(t) = G_{ik}Y_i(t)$ and $dN_{ik}(t) = G_{ik}dN_i(t)$. We assume that $\{N_i(t), Y_i(t), \mathbf{Z}_i(t), G_i\}_{i=1}^n$ are independent and identically distributed. For $d = 0, 1, 2$ and $k = 1, \dots, K$, let

$$\mathbf{S}_k^{(d)}(\beta, t) = n^{-1} \sum_{i=1}^n Y_{ik}(t) \mathbf{Z}_i(t)^{\otimes d} \exp\left\{\beta^T \mathbf{Z}_i(t)\right\},$$

$$\bar{\mathbf{Z}}_k(\beta, t) = \mathbf{S}_k^{(1)}(\beta, t) / \mathbf{S}_k^{(0)}(\beta, t),$$

$$\mathbf{V}_k(\beta, t) = \mathbf{S}_k^{(2)}(\beta, t) / \mathbf{S}_k^{(0)}(\beta, t) - \bar{\mathbf{Z}}_k(\beta, t)^{\otimes 2}$$

where $\mathbf{a}^{\otimes 0} = 1$, $\mathbf{a}^{\otimes 1} = \mathbf{a}$, and $\mathbf{a}^{\otimes 2} = \mathbf{a}\mathbf{a}^T$ for a vector $\mathbf{a}$.

Under the independent left truncation and right censoring assumptions, an unbiased estimating function for β is given by

$$\sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ \mathbf{Z}_i(t) - \bar{\mathbf{Z}}_k(\beta, t) \right\} dM_{ik}(t), \quad (5)$$

where

$$dM_{ik}(t) = dN_{ik}(t) - Y_{ik}(t) \exp\left\{\beta_0^T \mathbf{Z}_i(t)\right\} \theta_k d\mu_0(t).$$

We simplify (5) to

$$\mathbf{U}(\beta) = \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \left\{ \mathbf{Z}_i(t) - \bar{\mathbf{Z}}_k(\beta, t) \right\} dN_{ik}(t), \quad (6)$$

so that an estimator $\hat{\beta}$ of β can be obtained by solving $\mathbf{U}(\beta) = 0$. Schaubel and Cai (2005b) derived the large sample properties for $\hat{\beta}$ under the setting that $K \rightarrow \infty$. Theoretical results for $\hat{\beta}$ under the setting that $n \rightarrow \infty$ can be similarly obtained.

The Breslow-Alen type estimator of $\mu_{0k}(t) = \theta_k \mu_0(t)$ for $k = 1, \dots, K$ are

$$\hat{\mu}_{0k}(t)(\hat{\beta}, t) = n^{-1} \sum_{i=1}^n \int_0^t \frac{dN_{ik}(s)}{\mathbf{S}_k^{(0)}(\hat{\beta}, s)}.$$

With $\mu_{0k}(t) = \theta_k \mu_0(t)$, our chief interest is focused on $\mu_0(t)$ and θ_k , $k = 1, \dots, K$. Under the constraint for θ_k 's in model (2), $\sum_{k=1}^K w_k \theta_k = 1$, it follows that

$$\sum_{k=1}^K \{w_k \theta_k \mu_0(t)\} = \mu_0(t).$$

Therefore, a natural estimator of $\mu_0(t)$ is

$$\hat{\mu}_0(\hat{\beta}, t) = \sum_{k=1}^K w_k \hat{\mu}_{0k}(\hat{\beta}, t). \quad (7)$$

Next, we consider estimation for θ_k in model (2). From (4), we have that

$$E\{dN_{ik}(t) | G_i=k, \mathbf{Z}_i(t), Y_{ik}(t)\} = Y_{ik}(t) \exp\{\beta_0^T \mathbf{Z}_i(t)\} \theta_k d\mu_0(t).$$

It then follows by averaging over n on both sides of the above equation that

$$n^{-1} \sum_{i=1}^n E\{dN_{ik}(t) | G_i=k, \mathbf{Z}_i(t), Y_{ik}(t)\} = \theta_k d\mu_0(t) \mathbf{S}_k^{(0)}(\beta_0, t).$$

Thus, a natural estimator for θ_k is

$$\hat{\theta}_k = \frac{\overline{N}_k(\tau)}{\int_0^\tau \mathbf{S}_k^{(0)}(\hat{\beta}, t) d\hat{\mu}_0(\hat{\beta}, t)}, \quad (8)$$

where $\overline{N}_k(\tau) = n^{-1} \sum_{i=1}^n \int_0^\tau dN_{ik}(t) = n^{-1} \sum_{i=1}^n N_{ik}(\tau)$. This estimator $\hat{\theta}_k$ has a standardized ratio format, specifically, the numerator is the observed number of events up to time τ , and the denominator is the estimated expected number of events based on a (weighted) average center effect for subjects with characteristics and at risk patterns as are observed in the k th center.

Finally, we consider an alternative estimator based directly on the Model (3). In order to avoid identifiability problem, investigators usually choose a reference center and estimate the difference between the selected center effects and the reference level. With center r as the reference center, the estimators $\tilde{\eta}_k$ from Model (3) can be thought of as estimating $\eta_k - \eta_r$ with $\tilde{\eta}_r = 0$. Since the reference level under model (2) is $\sum_{k=1}^K w_k \theta_k$ and $\exp(\eta_k) = \theta_k$, an alternative estimator for θ_k is

$$\tilde{\theta}_k = \frac{\exp(\tilde{\eta}_k + \eta_r)}{\sum_{k=1}^K w_k \exp(\tilde{\eta}_k + \eta_r)}. \quad (9)$$

In terms of deriving large-sample properties, it is useful to re-write this estimator as

$$\tilde{\theta}_k = f_k(\tilde{\eta}^r) \quad (10)$$

where $\tilde{\eta}^r = (\tilde{\eta}_1, \dots, \tilde{\eta}_K)^T$ and

$$f_k(x_1, \dots, x_K) = \frac{\exp(x_k)}{\sum_{k=1}^K w_k \exp(x_k)}.$$

4 Asymptotic Results

To derive large sample properties of the parameters of interest, we first impose the following regularity conditions for $i = 1, \dots, n$ and $k = 1, \dots, K$.

- (a) $\{N_i(t), Y_i(t), \mathbf{Z}_i(t), G_i\}_{i=1}^n$ are independent and identically distributed;
- (b) $E\{Y_i(t)\} > 0$, for all $t \in (0, \tau]$;
- (c) $N_{ik}(\tau)$ are bounded;
- (d) $\mathbf{Z}_i(\cdot)$ have bounded total variations, i.e. $|\mathbf{Z}_{ij}(0)| + \int_0^\tau |d\mathbf{Z}_{ij}(t)| < c_Z < \infty$ for all $j = 1, \dots, p$, where $\mathbf{Z}_{ji}(\cdot)$ is the j th component of $\mathbf{Z}_i(\cdot)$ and c_Z is a constant;
- (e) $\mu_0(\tau)$ is bounded;
- (f) $P\{G_i = k\} > 0$;
- (g) There exists a neighborhood $\mathcal{B}$ of β_0 such that the following hold. For $d = 0, 1, 2$ and $k = 1, \dots, K$, $s_k^{(d)}(\beta, t)$ is a continuous function of $\beta \in \mathcal{B}$ uniformly in $t \in [0, \tau]$, where $s_k^{(d)}(\beta, t)$ is the limiting values of $\mathbf{S}_k^{(d)}(\beta, t)$; functions $s_k^{(1)}(\beta, t)$ and $s_k^{(2)}(\beta, t)$ are bounded and $s_k^{(0)}(\beta, t)$ is bounded away from 0 on $\mathcal{B} \times [0, \tau]$ with

$$s_k^{(1)}(\beta, t) = \frac{\partial}{\partial \beta} s_k^{(0)}(\beta, t), s_k^{(2)}(\beta, t) = \frac{\partial^2}{\partial \beta \partial \beta^T} s_k^{(0)}(\beta, t).$$

- (h) Positive-definiteness of the matrix

$$\mathbf{A} = \sum_{k=1}^K \int_0^\tau \mathbf{v}_k(\beta_0, t) s_k^{(0)}(\beta_0, t) \theta_k d\mu_0(t),$$

where $\mathbf{v}_k(\beta, t) = s_k^{(2)}(\beta, t) / s_k^{(0)}(\beta, t) - \bar{\mathbf{Z}}_k(\beta, t)^{\otimes 2}$ and

$$\bar{\mathbf{Z}}_k(\beta, t) = \mathbf{S}_k^{(1)}(\beta, t) / s_k^{(0)}(\beta, t).$$

In essence, we are considering a situation in which individuals arrive at the whole system at random over time yielding the iid structure in assumption a). The i th individual is assigned to center k with probability $P(G_i = k) > 0$ which is constant for all individuals. As a consequence, $n_k \rightarrow \infty$ as $n \rightarrow \infty$. Note, however, that the covariate vectors or censoring could depend on the facility assignment k . It is this iid structure that enables the asymptotic results to be derived and such assumptions are common in dealing with marginal type models as are being considered here. Other conditions are fairly familiar in the context of

regularity conditions for the Cox model. Condition (h), for example, would be violated if there were redundancies in the covariate vector.

We now describe the asymptotic properties of $\hat{\mu}_0(\hat{\beta}, t)$.

Theorem 1 Under regularity conditions (a) – (h), $\hat{\mu}_0(\hat{\beta}, t)$ converges almost surely to $\mu_0(t)$, uniformly in $t \in [0, \tau]$; $n^{1/2} \left\{ \hat{\mu}_0(\hat{\beta}, t) - \mu_0(t) \right\}$ converges in distribution to a Gaussian process with covariance function $\xi(s, t) = E\{\Phi_i(\beta_0, s)\Phi_i(\beta_0, t)\}$, where

$$\Phi_i(\beta, t) = \mathbf{h}(\beta, t)^T \mathbf{A}^{-1} \Psi_{1i}(\beta) + \Psi_{2i}(\beta, t),$$

$$\mathbf{h}(\beta, t) = - \sum_{k=1}^K w_k \int_0^t \bar{\mathbf{z}}_k(\beta, s) \theta_k d\mu_0(s),$$

$$\Psi_{1i}(\beta) = \sum_{k=1}^K \int_0^\tau \left\{ \mathbf{z}_i(t) - \bar{\mathbf{z}}_k(\beta, t) \right\} dM_{ik}(t)$$

$$\Psi_{2i}(\beta, t) = \sum_{k=1}^K w_k \int_0^t s_k^{(0)}(\beta, s)^{-1} dM_{ik}(\beta, s),$$

$$M_{ik}(\beta, t) = N_{ik}(t) - \int_0^t Y_{ik}(s) \exp\left\{\beta^T Z_i(s)\right\} \theta_k d\mu_0(s).$$

In the Appendix, we prove that $\xi(s, t)$ can be consistently estimated by

$\hat{\xi}(s, t) = n^{-1} \sum_{i=1}^n \left\{ \hat{\Phi}_i(\hat{\beta}, s) \hat{\Phi}_i(\hat{\beta}, t) \right\}$ with $\hat{\Phi}_i(\hat{\beta}, t)$ obtained by replacing all limiting values in $\Phi_i(\beta_0, t)$ with their empirical counterparts and replacing $\theta_k \mu_0(t)$ with $\hat{\mu}_{0k}(\hat{\beta}, t)$.

Next, we establish the asymptotic properties for $\hat{\theta}_k$.

Theorem 2 For $k = 1, \dots, K$, under conditions (a) – (h), $\hat{\theta}_k \rightarrow \theta_k$ almost surely as $n \rightarrow \infty$; $n^{1/2}(\hat{\theta}_k - \theta_k)$ is asymptotically normally distributed with mean zero and covariance $\Sigma_k = E\{\Gamma_{ki}(\beta_0)^2\}$, where

$$\Gamma_{ki}(\beta_0) = P_{ki}^1(\beta_0) + P_{ki}^2(\beta_0) + P_{ki}^3(\beta_0),$$

$$P_{ki}^1(\beta_0) = -\theta_k^2 E[N_{ik}(\tau)]^{-1} \left\{ \int_0^\tau s_k^{(1)}(\beta_0, t) d\mu_0(t) + \int_0^\tau s_k^{(0)}(\beta_0, t) d\mathbf{h}(\beta_0, t) \right\}^T \mathbf{A}^{-1} \Psi_{1i}(\beta_0),$$

$$P_{ki}^2(\beta_0) = -\theta_k^2 E[N_{ik}(\tau)]^{-1} \int_0^\tau s_k^{(0)}(\beta_0, t) d\Psi_{2i}(\beta_0, t),$$

$$P_{ki}^3(\beta_0) = \theta_k E[N_{ik}(\tau)]^{-1} \int_0^\tau dM_{ik}(\beta_0, t).$$

In the Appendix, we prove that Σ_k can be consistently estimated by $\hat{\Sigma}_k$, where

$\hat{\Sigma}_k = n^{-1} \sum_{i=1}^n \hat{\Gamma}_{ki}^2(\hat{\beta})$ with $\hat{\Gamma}_{ki}(\hat{\beta})$ obtained by replacing all limiting values in $\Gamma_{ki}(\beta_0)$ with their empirical counterparts and replacing $\theta_k \mu_0(t)$ with $\hat{\mu}_{0k}(\hat{\beta}, t)$.

The consistency of $\tilde{\theta}_k$ follows from the Slutsky's theorem and the known large sample properties of the regression parameters under the proportional rates model (Lin et al 2000). Its asymptotic distribution can be obtained using the delta method. Specifically, let $\theta = (\theta, \dots, \theta_K)^T$ and let $\tilde{\theta}$ be the corresponding alternative estimator. It can be easily shown that $n^{1/2}(\tilde{\theta} - \theta)$ converges to a K -variate normal vector with mean zero and a covariance matrix which can be estimated as $\tilde{\Sigma} = \tilde{\mathbf{Q}}^T \tilde{\Omega} \tilde{\mathbf{Q}}$, where $\tilde{\mathbf{Q}}$ is a $K \times (K-1)$ matrix with the k -th row equal to the partial derivative of $f_k(\tilde{\eta}^r)$ (omitting the r -th argument) and $\tilde{\Omega}$ is the consistent estimator of the asymptotic covariance matrix for $\tilde{\eta}$, where $\tilde{\eta}$ is a $(K-1)$ -vector without the r -th element in $\tilde{\eta}^r$.

Comparisons between centers are often of interest. To compare centers k and l , an appropriate null hypothesis is $H_0: \theta_k = \theta_l$. We consider three test statistics based on $\hat{\theta}$, $\tilde{\theta}$ and $\tilde{\eta}$ respectively, where $\hat{\theta}$ is the proposed standardized ratio format estimator for θ . The first test statistics could be obtained by considering the asymptotic distribution for $n^{1/2}(\hat{\theta} - \theta)$.

According to Theorem 2, $n^{1/2}(\hat{\theta} - \theta)$ converges to a K -variate normal vector with mean zero and covariance matrix $\Sigma = E\{\Gamma_1(\beta_0)^{\otimes 2}\}$, where Γ_1 is a K -vector with the k th element equal to $\Gamma_{k1}(\beta_0)$. It can be easily shown that $\hat{\Sigma}$, a consistent estimator for Σ , can be obtained

similarly to $\hat{\Sigma}_k$ for Σ_k . The test statistic is then $\hat{T}_{kl} = e_{kl}^T (\hat{\theta} - \theta) / (n^{-1} e_{kl}^T \hat{\Sigma} e_{kl})^{1/2}$, where e_{kl} is a K -vector with the k -th element equal to 1, the l -th element equal to -1 and the remaining $K-2$ elements equal to 0. The second test statistic is based on $\tilde{\theta}$, the proposed alternative estimator obtained through transformation of $\tilde{\eta}$. It is

$\tilde{T}_{kl}^\theta = e_{kl}^T (\tilde{\theta} - \theta) / (n^{-1} e_{kl}^T \tilde{\Sigma} e_{kl})^{1/2}$. The third test statistics is the Wald statistic for $\tilde{\eta}_k$, the estimator for $\eta_k - \eta_l$ obtained from the commonly used methods with reference center l .

This yields $\tilde{T}_{kl}^\eta = e_{kl}^T (\tilde{\eta} - \eta) / (n^{-1} e_{kl}^T \tilde{\Omega} e_k)^{1/2}$, where $\mathbf{e}_k$ is a $(K-1)$ -vector with k -th element equal to 1 and the rest equal to 0.

SAS code for carrying out the methods proposed in this section is available from the first author upon request.

5 Simulation

In this section, we assess the finite sample properties of the proposed estimator $\hat{\theta}_k$ through a series of simulation studies. Recurrent event data are simulated from the conditional Poisson model

$$E\{dN_i^*(t) | G=k, Z_i, D \geq t, W_i\} = W_i \exp\left\{\beta_0^T Z_i\right\} \theta_k d\mu_0(t), \quad (11)$$

where W_i follows a gamma distribution with mean 1 and variance 0.5, Z_i follows a Bernoulli distribution with $P(Z_i = 1) = 0.5$, $\beta_0 = 0.5$, and $\mu_0(t) = 0.5t$. The censoring time is fixed at 3 and the death time $D_i \sim U(0, 9)$. For the first 12 centers, we consider the combination of $\theta_k = 0.5, 1, 1.5$ and $n_k = 20, 50, 100, 200$. The remaining centers have center effect alternating among 0.5, 1, and 1.5. The total number of centers is always a multiple of three so that the weighted averaged center effect equals 1 with weights $w_k = 1/K$. Obviously, model (11) satisfies model (2). We consider $K = 30, 60, 150$.

We compare the two proposed estimators (8) and (10). The results shown in Table 1 are based on 1000 replicates. We report the bias of the sampling mean of the estimators (BIAS), the averaged standard error estimators (ASE), the empirical standard deviation of the estimators (ESD) and the 95% coverage probability (CP) for both $\hat{\theta}_k$ and $\tilde{\theta}_k$. In the last column, we report the empirical relative efficiency of $\tilde{\theta}_k$ with respect to $\hat{\theta}_k$ (ERE), which is calculated as the ratio of the squared ESD ($\hat{\theta}_k$) to the squared ESD ($\tilde{\theta}_k$). There is very little difference between the two estimators at least in the cases considered. Both are nearly unbiased and CPs become accurate as the center size increases. The results with $K = 150$ are similar to $K = 60$ and are not shown. As expected, the proposed standardized ratio format estimator does not outperform the transformed commonly used estimator since the partial likelihood estimator is semiparametric efficient. However, the proposed estimator is considerably more efficient in terms of computational time, which is important when the number of centers is very large. The times to compute 1000 replicates for $\hat{\theta}$ and $\tilde{\theta}$ are respectively 1.5 hours and 4 hours when $K = 30$, 2.5 hours and 17.33 hours when $K = 60$, and 8 hours and 150 hours when $K = 150$. The advantage of the standardized ratio format estimator, $\hat{\theta}$, becomes substantial as the number of centers increases (the ESRD data base has over 5000 centers). This is due to the fact that for $\hat{\theta}$, the dimension of the parameter space does not change with the number of centers, while it does change for $\tilde{\theta}$. Another important advantage of $\hat{\theta}$ is that it has the form of an observed frequency over an expected frequency, which is simple to describe to non-statistical personnel.

In the second simulation study, we compare the two estimators when the recurrent events and the terminating event are correlated. Specifically, we simulate $D_i = W_i D_i^1$ with $D_i^1 \sim U(0, 9)$. We keep the remaining settings the same as in the first simulation study. The results based on 1000 replicates are shown in Table 2. Similar to the first simulation study,

both estimators are unbiased with closed ESDs and ASEs. The coverage probabilities become closer to the nominal value as center size increases. Again, there is little difference between the two estimators except that $\hat{\theta}$ has remarkably shorter computation time.

6 Application

In this section, we apply the fixed center effect model to the dialysis patients hospital admission study and estimate the center effects using the proposed method. The hospital admission records are obtained using both national end-stage renal disease (ESRD) registry data and that from the Centers for Medicare and Medicaid Services (CMS). Patients are included in the study on day 91 since diagnosis of ESRD in order to assure that most patients are eligible for Medicare insurance either as their primary or secondary insurer. For illustrative purposes, we analyze hospital admission from dialysis patients treated in Michigan dialysis facilities in 2008. Therefore, the data are subject to left truncation (Jan. 1, 2008), a terminating event (death), and right censoring (Dec. 31, 2008 and loss to follow-up). In 2008, there was 482,440 dialysis patients treated in 5,363 Medicare-certified dialysis facilities in the U.S. and the facility sizes ranged from 1 to 566. The days of hospital admissions are recorded for each patient. The average number of hospital admissions per patient is 1.0.

We adjust for 5 patient characteristics: age, race, gender, ethnicity and diabetes. Patient age is categorized as 0–14, 15–24, 25–44, 45–59, 60–74, and over 74. Race is classified as African-American, Caucasian, Asian, Native-American and other. Ethnicity includes 3 levels, Hispanic, non-Hispanic and missing/unknown. Similarly, diabetes also includes three levels: diabetes, non-diabetes and missing/unknown. Under the proposed method, we estimate the center effects relative to the weighted average of center effect with the weights defined as the sampling proportion of each facility (n_k/n). In Figure 1, the estimated effects and the p-value from the one-sided test $H_0 : \theta_k > 1.3$ are plotted. There are 365 (6.81%) centers flagged with p-value less than 0.05.

Of interest is the detection of departures in admission rates from those 'expected' that are clinically significant. If we tested $H_0 : \theta_k = 1$, there would be the possibility of detecting a rather small (e.g. 5%) increase in the true hospitalization rate as statistically significant; this would be particularly true for large facilities. Testing against the null of 1.3 ensures that any differences detected as statistically significant are also clinically relevant. A second reason for considering hypotheses other than the sharp null is that there is generally natural variation among the facilities that may be due, for example, to unmeasured covariates that relate to patient outcomes and whose values vary across facilities. Allowing for the broader null also protects against this possibility. In fact, there is a substantial literature that is concerned with the issue of profiling facilities and of accounting appropriately for between facility variation. An excellent discussion and references can be found in Spiegelhalter and Grigg (2012). One approach that is sometimes suggested is based on the random effects model which incorporates explicitly the between facility variation. These approaches often suggest shrinkage estimators that adjust each facility's estimate by moving it toward the overall mean. It can be seen, however, that fixed effects provide a more accurate estimate of the true facility effect in more extreme cases and we prefer the approach of using the fixed

effects, but adjusting the methods of profiling to allow for this inherent deviation. Another approach can be based on the method of the empirical null discussed by Efron (2004), which also adjusts for natural between facility variation.

Note that the duration of hospitalization is not explicitly accounted for in our analysis of hospital admissions. The admission rate considered is the average rate at time t for patients with the given covariates and facility assignment, and as such it is averaged over patients in and out of the hospital.

7 Discussion

In this paper, we proposed an alternative estimator for center effects in the fixed center effect proportional rates model for recurrent event data. Both the absence and the presence of a terminal event are considered. The new estimator is the ratio of the observed number of recurrent events to the expected number based on a weighted average of center effects and the same patient mix. The new estimators perform as well as the appropriately transformed estimators obtained by including parameter for centers as a part of in the regression model. The proposed estimation procedure is computationally more efficient, since the dimension of the regression parameter space only depends on the number of adjustment. When the number of centers is large, such as large registry studies, the commonly used method may not be computationally feasible. In this case, particularly, the proposed estimator has substantial computational advantage. In addition, the standardization with respect to this multiplicative center effect θ_k instead of the additive center effect η_k within the exponential form appears to be novel and avoids the problems when $\hat{\eta}_k = -\infty$.

In the estimation and evaluation of center effects, concern is often raised regarding multiple testing. It is our view that issues of multiple testing should not arise in the problem of profiling facilities. Our analytic objective in Section 6 is to assess each facility separately and on its own merits; we thus think it appropriate to carry out separate tests without adjustment to the p-value despite implications on the global Type I error. In fact, we are not interested in the global null hypothesis where multiple testing might be important in controlling the overall type I error. From a patient's perspective, the Type II error is very important and our aim is to identify facilities where additional investigations may be appropriate. Adjustments for multiple testing would lead inappropriately to very high Type II error and patient risk.

Of the two proposed center effect measures, only that specified in (9) requires parametric assumptions [through reliance on model (2)] on the association between center and the event rate. As described in Section 3, the methods of estimation corresponding to model (2) have a strong connection to the Cox model. model (1) can be considered an extension of the model proposed by Lin, Wei, Yang, and Ying (2000); which has come to be known as the recurrent event analog of the Cox model. From this angle, proportionality could be evaluated with methods analogous to those employed to check the Cox model. For example, one could examine various residual plots over time. For a more objective and numerical evaluation, one could also test various facility $\times$ time interactions. In practice, the examination of the

plots would be tedious to carry out when the number of facilities is large. However, it would be feasible to code a macro or function to sequentially test facility-by-time interactions.

Another possible estimation method is based on the population averaged model, which can be obtained from (2) by integrating out G as

$$E \{dN^*(t) | \mathbf{Z}(t), D \geq t\} = \exp \left\{ \beta_0^T \mathbf{Z}(t) \right\} d\mu_0(t) \sum_{k=1}^K \theta_k P \{G=k | \mathbf{Z}(t), D \geq t\}.$$

If the distribution of G does not depend on patient characteristics and whether the patient is alive, i.e. $P \{G=k | \mathbf{Z}(t), D \geq t\} = P \{G=k\}$, the population averaged model still keeps the proportional rates format as

$$E \{dN^*(t) | \mathbf{Z}(t), D \geq t\} = \exp \left\{ \gamma_0^T \mathbf{Z}(t) \right\} d\mu_0^*(t), \quad (12)$$

where $d\mu_0^*(t) = d\mu_0(t) \sum_{k=1}^K \theta_k^* P \{G=k\} = d\mu_0(t)$ under the constraint that $\sum_{k=1}^K \theta_k^* P \{G=k\} = 1$. An estimator for $\mu_0(t)$ can be obtained from the marginal model with $\hat{\beta}^T(t)$ as an offset. An estimator for θ_k can then be obtained similar to $\hat{\theta}_k$. Under this condition, $d\mu_0(t)$ can be interpreted as the population averaged baseline rate function, and θ_k can be interpreted as the center effect relative to the population level. If, in practice, the distribution of G does not depend on $\mathbf{Z}(t)$ and is a constant over time, this estimator could be used without specifying the weight terms. For the motivating study, however, this condition may not be satisfied. For example, pediatric dialysis patients might more likely receive treatment from pediatric dialysis units.

The proposed method can be easily extended to the fixed center effect proportional hazards model for failure time data. Similarly, it can also be extended to other semiparametric models with appropriate constraint on the fixed center effect.

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Appendix

A.1 Consistency of $\hat{\mu}_0(\hat{\beta}, t)$

Let $\phi_0(t) = \hat{\mu}_0(\hat{\beta}, t) - \mu_0(t) = \phi_1(t) + \phi_2(t)$, where $\phi_1(t) = \hat{\mu}_0(\hat{\beta}, t) - \hat{\mu}_0(\beta, t)$ and $\phi_2(t) = \hat{\mu}_0(\beta, t) - \mu_0(t)$. By the triangle inequality,

$$\sup_{t \in [0, \tau]} |\phi_0(t)| \leq \sup_{t \in [0, \tau]} |\phi_1(t)| + \sup_{t \in [0, \tau]} |\phi_2(t)|. \quad (\text{A.1})$$

A Taylor series expansion of

$$\phi_1(t) = n^{-1} \sum_{i=1}^n \sum_{k=1}^K w_k \left\{ \int_0^t \frac{dN_{ik}(s)}{\mathbf{S}_k^{(0)}(\hat{\beta}, s)} - \int_0^t \frac{dN_{ik}(s)}{\mathbf{S}_k^{(0)}(\beta, s)} \right\}$$

yields

$$\phi_1(t) = H(\beta^\dagger, t)^T (\hat{\beta} - \beta_0) + o_p(n^{-1/2}),$$

where $\beta^\dagger$ lies in the line segment between $\hat{\beta}$ and β_0 , and $H(\beta, t) = n^{-1} \sum_{i=1}^n H_i(\beta, t)$, and

$$H_i(\beta, t) = - \sum_{k=1}^K w_k \int_0^t \frac{\bar{\mathbf{Z}}_k(\beta, s)}{\mathbf{S}_k^{(0)}(\beta, s)} dN_{ik}(s).$$

Since $N_{ik}(s)$, $\mathbf{S}_k^{(1)}(\beta, s)$ are bounded and $\mathbf{S}_k^{(0)}(\beta, s)$ is bounded away from 0 for $\beta \in \mathcal{B}$ and $s \in [0, \tau]$ as $n \rightarrow \infty$, it follows that $H(\beta, t) = n^{-1} \sum_{i=1}^n H_i(\beta, t)$ is bounded for sufficiently large n . Since $\hat{\beta} \xrightarrow{a.s.} \beta_0$ as $n \rightarrow \infty$, it follows that

$$\sup_{t \in [0, \tau]} |\phi_1(t)| \xrightarrow{a.s.} 0. \quad (\text{A.2})$$

Further, since $\sum_{k=1}^K w_k \theta_k = 1$, we find

$$\begin{aligned} \phi_2(t) &= \sum_{k=1}^K w_k \left\{ \sum_{i=1}^n \int_0^t \frac{dN_{ik}(s)}{n \mathbf{S}_k^{(0)}(\beta_0, s)} - \theta_k \mu_0(t) \right\} \\ &= \sum_{k=1}^K w_k \sum_{i=1}^n \int_0^t \frac{dN_{ik}(s) - Y_{ik}(s) \exp\{\beta_0^T \mathbf{Z}_i(s)\} \theta_k d\mu_0(s)}{n \mathbf{S}_k^{(0)}(\beta_0, s)} \\ &= n^{-1} \sum_{k=1}^K \sum_{i=1}^n w_k \int_0^t \frac{dM_{ik}(\beta_0, s)}{\mathbf{S}_k^{(0)}(\beta_0, s)}. \end{aligned}$$

Since $\mathbf{S}_k^{(0)}(\beta, s)$ is bounded away from 0 and $n^{-1} \sum_{i=1}^n \sum_{k=1}^K M_{ik}(\beta_0, s) \xrightarrow{a.s.} 0$ by the Strong Law of Large Numbers (SLLN) as $n \rightarrow \infty$ for $s \in [0, \tau]$, we have that

$$\sup_{t \in [0, \tau]} |\phi_2(t)| \xrightarrow{a.s.} 0. \quad (\text{A.3})$$

The uniform consistency of $\hat{\mu}_0(\hat{\beta}, t)$ follows from (A.1), (A.2) and (A.3).

A.2 Weak Convergence of $\hat{\mu}_0(\hat{\beta}, t)$

We now consider the process $n^{1/2}\phi_0(t) = n^{1/2}\phi_1(t) + n^{1/2}\phi_2(t)$. We see that

$$n^{1/2}\phi_1(t) = H(\beta_0, t)^T n^{1/2}(\hat{\beta} - \beta_0) + o_p(1)$$

$$n^{1/2}\phi_2(t) = n^{-1/2} \sum_{i=1}^n \hat{\Psi}_{2i}(\beta_0, t),$$

where $\hat{\Psi}_{2i}(\beta_0, t) = \sum_{k=1}^K w_k \int_0^t \mathbf{S}_k^{(0)}(\beta, 0)^{-1} dM_{ik}(\beta_0, s)$.

Under conditions (a) – (g), it follows that $\sup_{t \in [0, \tau]} |\hat{\mu}_{0k}(\hat{\beta}, t) - \mu_{0k}(t)| \xrightarrow{a.s.} 0$, $k = 1, \dots, K$, and $H(\beta_0, t) \xrightarrow{a.s.} h(\beta_0, t)$ for $t \in [0, \tau]$.

The partial likelihood score equation (6) can be written as

$$\mathbf{U}(\beta) = \sum_{i=1}^n \hat{\Psi}_i(\beta),$$

$$\hat{\Psi}_{1i}(\beta) = \sum_{k=1}^K \int_0^\tau \left\{ \mathbf{Z}_i(t) - \bar{\mathbf{Z}}_k(\beta, t) \right\} dM_{ik}(t).$$

Under condition (e), $\hat{\Psi}_{1i}(\beta)$ converges to $\Psi_{1i}(\beta)$ for $i = 1, \dots, n$. A Taylor series expansion of the score equation at $\hat{\Psi}_{1i}(\beta)$ around β_0 yields

$$\mathbf{U}(\beta_0) = \hat{I}(\beta_0) (\hat{\beta} - \beta_0) + o_p(n^{-1/2}),$$

$$\hat{I}(\beta_0) = \sum_{i=1}^n \sum_{k=1}^K \int_0^\tau \mathbf{V}_{ik}(t) dN_{ik}(t).$$

As $n \rightarrow \infty$, $n^{-1} \hat{I}(\beta_0) \xrightarrow{a.s.} \mathbf{A}$, where $\mathbf{A}$ is the positive definite matrix defined in condition (h). We can see that

$$n^{1/2}\phi_1(t) = h(\beta_0, t)^T A^{-1} n^{-1/2} \sum_{i=1}^n \Psi_{1i}(\beta_0) + o_p(1). \quad (\text{A.4})$$

Under condition (e), $\hat{\Psi}_{2i}(\beta_0, t)$ converges to $\Psi_{2i}(\beta_0, t)$ for $i = 1, \dots, n$. Hence

$$n^{1/2}\phi_2(t) = \sum_{i=1}^n \Psi_{2i}(\beta_0, t) + o_p(1). \quad (\text{A.5})$$

Combining (A.4) and (A.5), we see that $n^{1/2}\phi_0(t) = n^{-1/2}\sum_{i=1}^n \Phi(\beta_0, t) + o_p(1)$, which converges weakly to a Gaussian Process with covariance function ξ .

A.3 Consistency of $\hat{\theta}_k$

From (8),

$$\hat{\theta}_k - \theta_k = \frac{n^{-1}\sum_{i=1}^n \int_0^\tau [dN_{ik}(t) - Y_{ik}(t) \exp\{\hat{\beta}^T \mathbf{Z}_i(t)\} \theta_k d\hat{\mu}_0(\hat{\beta}, t)]}{\int_0^\tau \mathbf{S}_k^{(0)}(\hat{\beta}, t) d\hat{\mu}_0(\hat{\beta}, t)}. \quad (\text{A.6})$$

With the uniform consistency of $\hat{\beta}$ and $\hat{\mu}_0(\hat{\beta}, t)$ as $n \rightarrow \infty$,

$$n^{-1} \sum_{i=1}^n \left\{ \int_0^\tau Y_{ik}(t) \exp\{\hat{\beta}^T \mathbf{Z}_i(t)\} \theta_k d\hat{\mu}_0(\hat{\beta}, t) - \int_0^\tau Y_{ik}(t) \exp\{\beta_0^T \mathbf{Z}_i(t)\} \theta_k d\mu_0(\beta, t) \right\} \xrightarrow{a.s.} 0.$$

In addition,

$$n^{-1} \sum_{i=1}^n \int_0^\tau [dN_{ik}(t) - Y_{ik}(t) \exp\{\beta_0^T \mathbf{Z}_i(t)\} \theta_k d\mu_0(\beta, t)] = n^{-1} \sum_{i=1}^n \int_0^\tau dM_{ik}(\beta_0, t) \xrightarrow{a.s.} 0$$

by the SLLN as $n \rightarrow \infty$. Hence the numerator in (A.6) converges almost surely to 0 as $n \rightarrow \infty$. With the boundedness condition (c) and (e), the denominator in (A.6) is also bounded. Hence,

$$\hat{\theta}_k - \theta_k \xrightarrow{a.s.} 0.$$

A.4 Weak convergence of $\hat{\theta}_k$

Let $\zeta_k = \theta_k^{-1}$ and $\hat{\zeta}_k = \hat{\theta}_k^{-1}$ for $k = 1, \dots, K$. In the following, we will first show the asymptotic approximation of $n^{1/2}(\hat{\zeta}_k - \eta_k)$ and then use the delta method to obtain the asymptotic properties for $n^{1/2}(\hat{\theta}_k - \theta_k)$. Since

$$\begin{aligned} n^{1/2}(\hat{\eta}_k - \eta_k) &= n^{1/2} \left\{ \bar{N}_k(\tau)^{-1} \int_0^\tau S_k^{(0)}(\hat{\beta}, t) d\hat{\mu}_0(\hat{\beta}, t) - \theta_k^{-1} \right\} \\ &= n^{1/2} \bar{N}_k(\tau)^{-1} \theta_k^{-1} \int_0^\tau \left\{ S_k^{(0)}(\hat{\beta}, t) \theta_k d\hat{\mu}_0(\hat{\beta}, t) - d\bar{N}_k(t) \right\}, \end{aligned}$$

$n^{1/2}(\hat{\eta}_k - \eta_k)$ can be decomposed into three terms as

$$\begin{aligned} n^{1/2}(\hat{\eta}_k - \eta_k) &= n^{1/2} \bar{N}_k(\tau)^{-1} \int_0^\tau \left\{ S_k^{(0)}(\hat{\beta}, t) d\hat{\mu}_0(\hat{\beta}, t) - S_k^{(0)}(\beta_0, t) d\hat{\mu}_0(\beta_0, t) \right\} \\ &\quad + n^{1/2} \bar{N}_k(\tau)^{-1} \int_0^\tau S_k^{(0)}(\beta_0, t) \{d\hat{\mu}_0(\beta_0, t) - d\mu_0(t)\} \\ &\quad + n^{1/2} \bar{N}_k(\tau)^{-1} \theta_k^{-1} \int_0^\tau \left\{ S_k^{(0)}(\beta_0, t) \theta_k d\mu_0(t) - d\bar{N}_k(t) \right\}. \end{aligned} \quad (\text{A.7})$$

A Taylor series expansion of the first term of the right-hand side of equation (A.7) equals

$$n^{1/2} \bar{N}_k(\tau)^{-1} \left\{ \int_0^\tau \mathbf{S}_k^{(1)}(\beta^\dagger, t) d\hat{\mu}_0(\beta^\dagger, t) + \int_0^\tau S_k^{(0)}(\beta^\dagger, t) dH(\beta^\dagger, t) \right\}^\tau (\hat{\beta} - \beta_0),$$

where $\beta^\dagger$ is on the line segment between $\hat{\beta}$ and β_0 . With the results in A.2, condition (e) and the uniform consistency of $\hat{\beta}$ and $\hat{\mu}_0(\hat{\beta}, t)$, the first term of the right-hand side of equation (A.7) equals

$$n^{-1/2} E[N_{ik}(\tau)]^{-1} \left\{ \int_0^\tau s_k^{(1)}(\beta_0, t) d\mu_0(t) + \int_0^\tau s_k^{(0)}(\beta_0, t) dh(\beta_0, t) \right\}^\tau A^{-1} \sum_{i=1}^n \Psi_{1i}(\beta_0) + o_p(1) \quad (\text{A.8})$$

With the results in (A.1) and condition (e), the second term of the right-hand side of equation (A.7) equals

$$n^{-1/2} E[N_{ik}(\tau)]^{-1} \sum_{i=1}^n \int_0^t s_k^{(0)}(\beta_0, t) d\Psi_{2i}(\beta_0, t) + o_p(1). \quad (\text{A.9})$$

The third term of the right-hand side of equation (A.7) equals

$$n^{-1/2} E[N_{ik}(\tau)]^{-1} \theta_k^{-1} \sum_{i=1}^n \int_0^t dM_{ik}(\beta_0, t) + o_p(1). \quad (\text{A.10})$$

Combining (A.7), (A.8), (A.9) and (A.10), we see that

$$n^{1/2} (\hat{\eta}_k - \eta_k) = -n^{1/2} \sum_{i=1}^n -\zeta_k^2 \Gamma_{ki}(\beta_0) + o_p(1).$$

Therefore, $n^{1/2} (\hat{\eta}_k - \eta_k)$ converges in distribution to a normal variable with mean 0 and variance is asymptotically $E\{\zeta^4 \Gamma_{ki}(\beta_0)^2\}$. Since $\hat{\theta}_k = 1/\hat{\zeta}_k$, applying the delta method, we have that $n^{1/2} (\hat{\theta}_k - \theta_k)$ is asymptotically normally distributed with mean 0 and covariance $\Sigma_k = E\{\Gamma_{ki}(\beta_0)^2\}$.

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Fig. 1. Scatter plot of estimated center effect from the proposed method and the corresponding p-value for $H_0 : \theta_k > 1.3$.

Results of the first simulation study with $\beta = 0.5$, $\mu_{0k}(t) = 0.5t$ and 1000 replicates comparing the proposed standardized ratio format estimator defined in (8): $\hat{\theta}_{kr}$ and the alternative estimator defined in (9): $\tilde{\theta}_k$. Shown below are bias, empirical standard deviation (ESD), the averaged standard error estimators (ASE) and the 95 % coverage probability (CP) of the estimators as well as the empirical relative efficiency (ERE) of $\hat{\theta}_k$ with respect to $\tilde{\theta}_k$.

Table 1

K	n _k	θ _k	$\hat{\theta}_k$				$\tilde{\theta}_k$				
			BIAS	ASE	ESD	CP	BIAS	ASE	ESD	CP	ERE
30	20	0.5	-0.002	0.140	0.154	0.892	-0.002	0.140	0.154	0.895	1.000
		1	-0.002	0.221	0.236	0.907	-0.002	0.222	0.236	0.908	0.991
		1.5	-0.012	0.295	0.323	0.903	-0.012	0.296	0.323	0.903	0.993
	50	0.5	-0.001	0.092	0.095	0.931	-0.001	0.092	0.095	0.929	1.000
		1	-0.004	0.146	0.146	0.930	-0.004	0.146	0.146	0.930	1.000
		1.5	-0.001	0.198	0.208	0.926	-0.001	0.199	0.208	0.925	0.990
	100	0.5	0.002	0.067	0.067	0.950	0.002	0.067	0.067	0.951	1.000
		1	0.004	0.108	0.102	0.959	0.004	0.108	0.102	0.957	1.000
		1.5	-0.010	0.145	0.150	0.935	-0.010	0.145	0.150	0.935	1.000
60	200	0.5	0.001	0.049	0.047	0.946	0.000	0.049	0.047	0.946	1.000
		1	0.008	0.080	0.085	0.942	0.008	0.080	0.085	0.942	1.000
		1.5	0.000	0.108	0.107	0.947	0.000	0.108	0.107	0.946	1.000
	20	0.5	-0.002	0.141	0.155	0.892	-0.002	0.141	0.155	0.893	1.000
		1	-0.002	0.225	0.240	0.908	-0.002	0.226	0.240	0.910	0.991
		1.5	-0.011	0.301	0.329	0.909	-0.011	0.302	0.329	0.910	0.993
	50	0.5	-0.002	0.092	0.095	0.930	-0.001	0.092	0.095	0.930	1.000
		1	-0.004	0.147	0.148	0.929	-0.004	0.147	0.148	0.929	1.000
		1.5	-0.001	0.201	0.213	0.922	-0.001	0.201	0.213	0.923	1.000
100	200	0.5	0.002	0.067	0.067	0.945	0.002	0.067	0.067	0.946	1.000
		1	0.003	0.108	0.102	0.961	0.003	0.108	0.102	0.960	1.000
		1.5	-0.011	0.146	0.150	0.939	-0.011	0.146	0.150	0.938	1.000
	20	0.5	0.000	0.048	0.046	0.952	0.000	0.048	0.046	0.952	1.000
		1	0.007	0.078	0.084	0.947	0.007	0.078	0.084	0.945	1.000
		1.5	-0.001	0.106	0.105	0.944	-0.001	0.106	0.105	0.946	1.000

Table 2

Results of the second simulation study with $\beta = 0.5$, $\mu_{0K}(t) = 0.5t$ and 1000 replicates comparing the proposed standardized ratio format estimator $\hat{\theta}_k$ and the transformed commonly used estimator $\tilde{\theta}_k$. Shown below are bias, empirical standard deviation (ESD), the averaged standard error estimators (ASE) and the 95 % coverage probability (CP) of the estimators as well as the empirical relative efficiency (ERE) of $\hat{\theta}_k$ with respect to $\tilde{\theta}_k$.

K	n_k	θ_k	$\hat{\theta}_k$				$\tilde{\theta}_k$			
			BIAS	ASE	ESD	CP	BIAS	ASE	ESD	CP
30	20	0.5	-0.001	0.135	0.149	0.893	-0.001	0.136	0.149	0.892
		1	-0.000	0.210	0.228	0.906	0.001	0.211	0.228	0.907
	1.5	0.5	-0.018	0.279	0.304	0.896	-0.016	0.280	0.305	0.898
		1	-0.003	0.089	0.093	0.924	-0.003	0.089	0.093	0.925
	50	0.5	-0.005	0.139	0.137	0.941	-0.003	0.139	0.138	0.939
		1	-0.005	0.185	0.199	0.919	-0.003	0.186	0.199	0.919
100	20	0.5	0.005	0.065	0.066	0.934	0.006	0.065	0.066	0.933
		1	0.004	0.104	0.103	0.943	0.006	0.104	0.104	0.943
	1.5	0.5	-0.006	0.138	0.138	0.948	-0.004	0.138	0.138	0.951
		1	0.001	0.047	0.047	0.942	0.002	0.047	0.047	0.940
	200	0.5	0.008	0.076	0.078	0.942	0.009	0.076	0.078	0.940
		1	-0.004	0.102	0.102	0.952	-0.002	0.102	0.102	0.953
60	20	0.5	-0.001	0.136	0.150	0.892	-0.001	0.136	0.150	0.893
		1	0.000	0.213	0.232	0.907	0.001	0.214	0.232	0.911
	1.5	0.5	-0.017	0.285	0.309	0.895	-0.015	0.287	0.310	0.896
		1	-0.004	0.089	0.093	0.921	-0.003	0.089	0.093	0.923
	50	0.5	-0.005	0.140	0.139	0.940	-0.004	0.140	0.139	0.939
		1	-0.005	0.188	0.204	0.905	-0.003	0.188	0.204	0.907
200	20	0.5	0.005	0.065	0.066	0.932	0.006	0.065	0.066	0.933
		1	0.004	0.103	0.104	0.943	0.005	0.104	0.104	0.943
	1.5	0.5	-0.006	0.138	0.140	0.948	-0.004	0.138	0.141	0.947
		1	0.001	0.047	0.046	0.944	0.002	0.047	0.046	0.944
	200	0.5	0.007	0.075	0.076	0.939	0.008	0.075	0.077	0.939
		1	-0.005	0.100	0.100	0.948	-0.003	0.101	0.100	0.945