# ZIKQ: An innovative centile chart method for utilizing natural history data in rare disease clinical development

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**Supplementary Material**

## S1 Bandwidth selection

We explored some available options for bandwidth computing:

1. the `dpill` function in `R` package `KernSmooth` implemented the method of Ruppert et al. (1995) to calculate a direct plug-in estimator for $h_{mean}$

2. the `h.amise` function in `R` package `kedd` evaluates the asymptotic mean integrated squared error to choose $h_{mean}$ (Terrell and Scott, 1985).

3. the `bw.nrd0` function in `R` package `stats` implements a rule-of-thumb for choosing the bandwidth of a Gaussian kernel density estimator (Silverman, 1986).

In addition, we also explore user-provided $h_{mean}$ or the entire sequence $h_\tau$. The corresponding results are presented in Figure 1. In general, the choice of bandwidth does not affect the estimation that much. In the paper, we use `KernSmooth` with the function `dpill`, as suggested in Yu and Jones (1998).

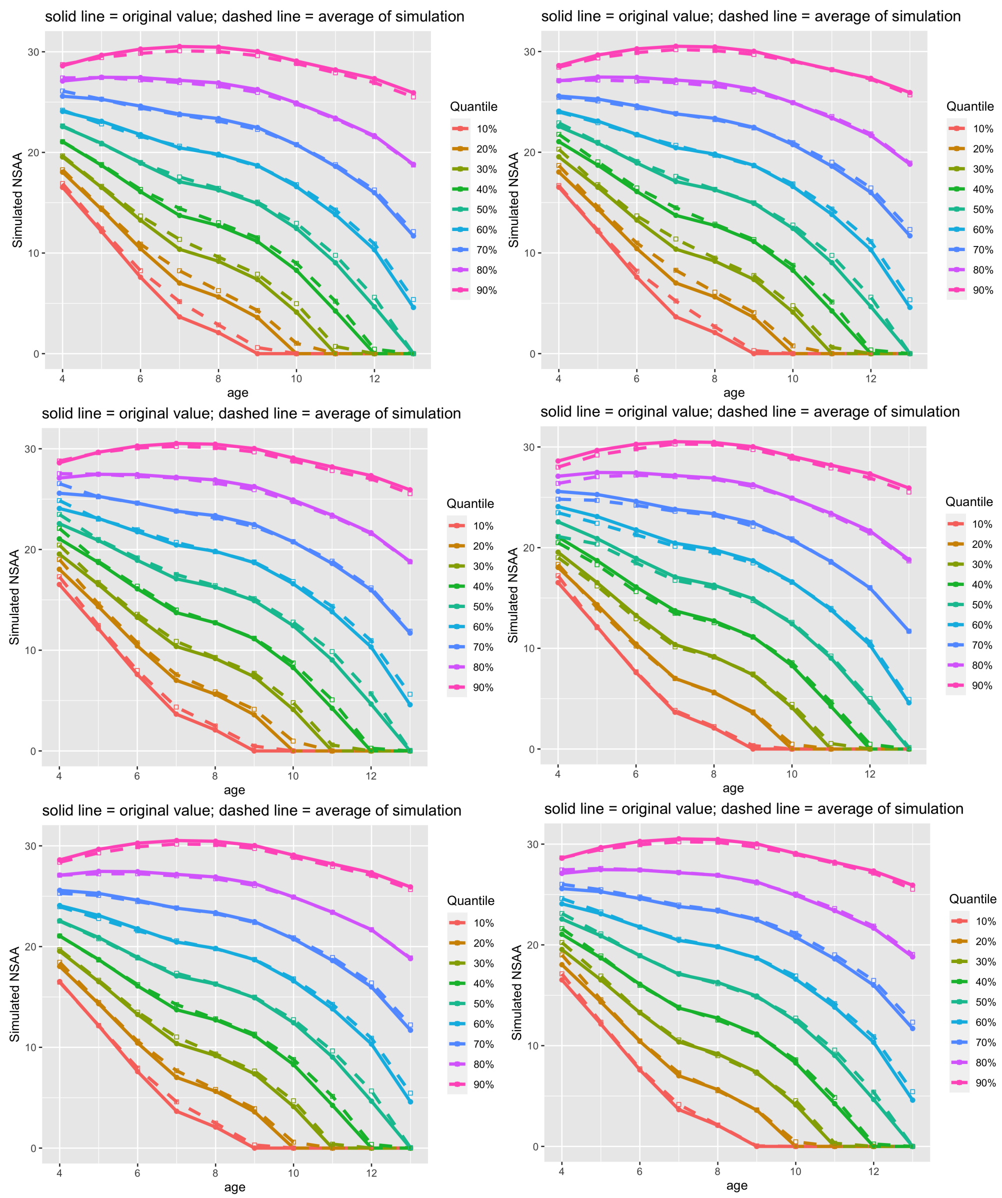


Figure 1: Simulation results for the proposed method with different methods selecting bandwidth $h_{mean}$): (1) `KernSmooth` package(top left, $\bar{h}_{mean} \approx 0.7$), (2) `kedd` package(top right, $\bar{h}_{mean} \approx 0.8$), (3) `stats` package function `bw.nrd0`(mid left, $\bar{h}_{mean} \approx 0.32$), (4) `stats` package function `bw.ucv`(mid right, $\bar{h}_{mean} \approx 0.15$), (5) user input $h_{mean} = 0.5$ (bottom left). After obtain $h_{mean}$, we obtain all other $h_\tau = h_{mean}\{\tau(1-\tau)/\phi(\Phi^{-1}(\tau))^2\}^{1/5}$. (6) set all $h_\tau = 0.5$ (bottom right).

## S2 Additional simulation studies

We present three additional simulation settings in this section: (1) irregular observed time points, (2) $Y$ is generated from a stochastic process rather than mimicking the natural history data, and (3) compares the traditional KM estimate with the proposed KM estimate.

To generate data with irregular observational age, we first generate a starting age $t_{i1} \sim \text{Unif}(4, 13)$ for each subject, which is the same as described in Section 4. Then, for the following observations per person, instead of setting $t_{ij} = t_{i1} + 0.5(j-1)$, we set $t_{ij} = t_{i1} + \Delta_j$ with $\Delta_j \sim N(0.5(j-1), 0.2^2)$. That is, we assume each subject visits the hospital at around half a year but not exactly. When the observational ages are irregular, the proposed method still works satisfactorily (see Figure 2), with the estimation at each time point on the chart being rounded to a grid of age.

Then, we consider the second case, in which $Y$ is generated by a stochastic process instead of mimicking the natural history data. We first simulate the grid of $t$ based on an original observation $t_0$, as described in Section 4. Then, we generate $\mu(t) = -0.2t^2 + 1.2t + 10$ and $Y(t) = N(\mu(t), 3^2)$. The true centile curves (denoted by solid lines in Figure 3) are obtained by generating a large sample $10^5$ to mimic the population and then applying

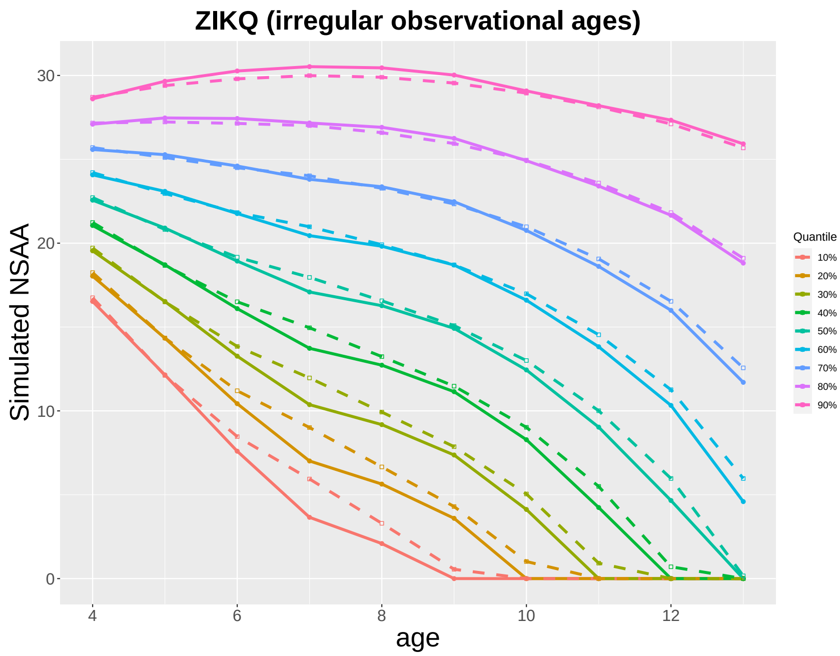


Figure 2: Estimation results of ZIKQ with irregular observation points. The solid line represents the true value, and the dashed line represents the average of estimated values.

ZIKQ. Results suggest that the proposed method estimates the true curves consistently.

Next, we compare the estimation of the proposed KM estimator and the classical KM estimator with 100 Monte Carlo replicates. The data-generating scheme is the same as described in Section 4 of the paper. In Figure 4, we provide the average of $\hat{S}(t)$ with $n_r = d_r + c_r + s_r$ (blue line) and the average of estimated $\hat{S}(t)$ by the classical KM estimator with $n_r = n_{r-1} - d_{r-1} - c_{r-1}$ (red line). Compared to the true $S(t)$ (black line),

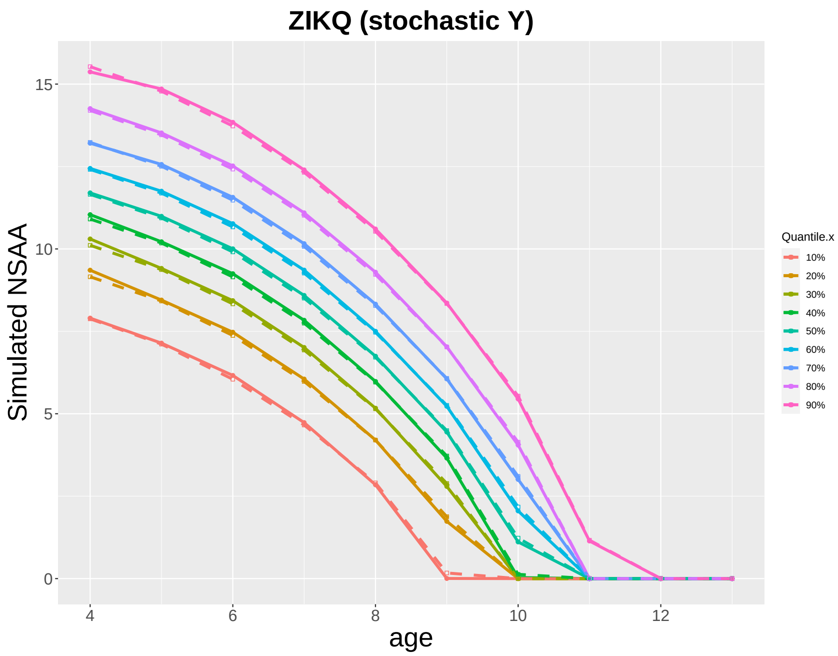


Figure 3: Estimation results of ZIKQ with $Y$ generated from a stochastic process. The solid line represents the true value, and the dashed line represents the average of estimated values.

the classical KM estimator has an obvious deviation from the truth when approaching older age.

## S3 Estimated centile chart with confidence intervals

Though the estimated chart itself is always the primary consideration in practice, such as the use of a growth chart, the confidence interval is often of interest from a statistical perspective. In this section, we illustrate con-

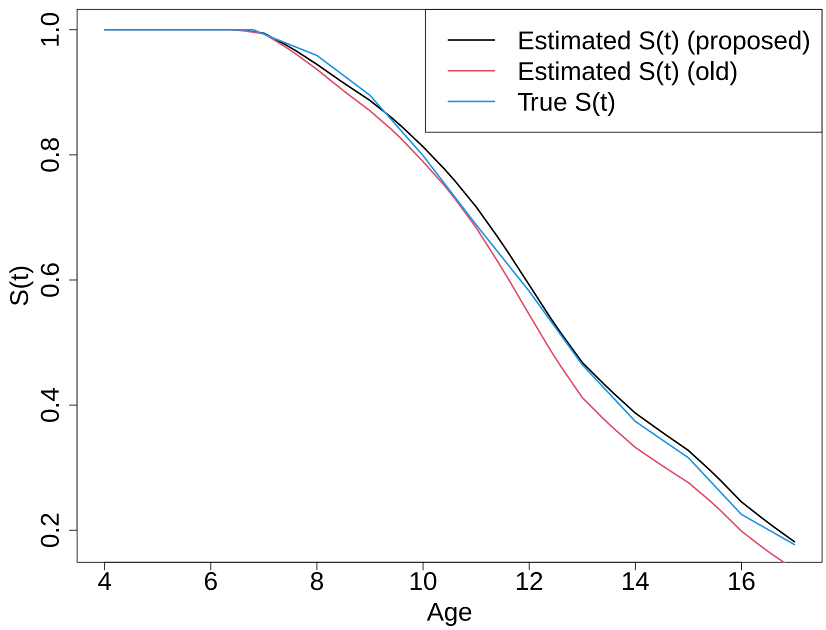


Figure 4: Compare the estimation of $S(t)$ by the proposed KM estimator and the classical KM estimator.

fidence intervals for the estimated centile chart can be easily built based on Bootstrap. As every individual consists of multiple observations, we resample individuals with replacement instead of resample observations. Then, the regular procedure is conducted to estimate the chart, and the 97.5% and 2.5% quantiles of the empirical distribution from bootstrap are reported at each time point. For better visualization, we report estimated curves at 10%, 30%, 50%, 70%, and 90% (Figure 5). The confidence intervals are well-separated with narrow widths, indicating the validity of the proposed approach.

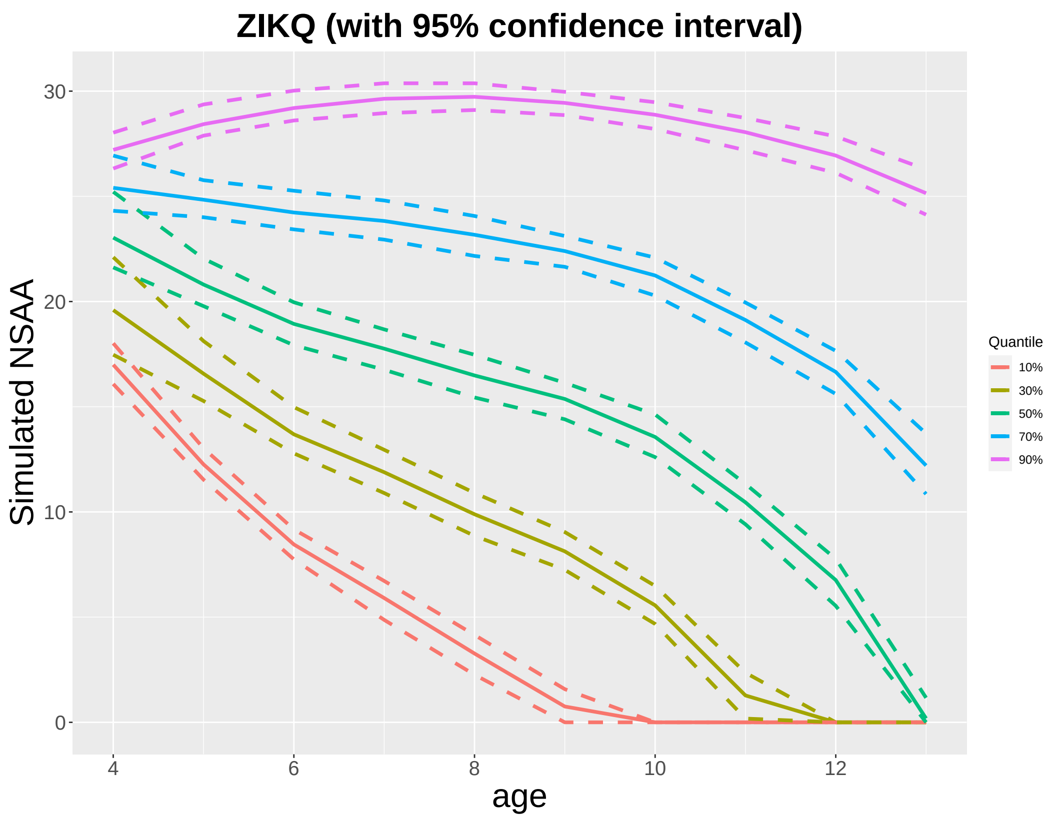


Figure 5: Estimated centile chart by ZIKQ with confidence intervals. Solid lines represent the estimated chart, and dashed lines indicate 95% confidence intervals based on Bootstrap.

## S4 Proof for Theorem 1

*Proof.* We show the consistency of $\hat{Q}_Y(\tau \mid t)$ under two scenarios: $\tau \leq 1 - S(t)$ and $\tau > 1 - S(t)$ for its piecewise nature. As the true $S(t)$ is unobserved, given the estimated function $\hat{S}(\cdot)$ and observational time $T = t$, the probability of observing a positive response $Y$ is estimated as $\hat{S}(t)$. Then, we divide the support of quantile levels $(0, 1)$ of $Y$ into two intervals such that $(0, 1) = A_n \cup B_n$:

$$
\begin{aligned}
A_n &= \left\{\tau : 0 < \tau \leq 1 - \hat{S}(t)\right\}, \\
B_n &= \left\{\tau : 1 - \hat{S}(t) < \tau \leq 1\right\}.
\end{aligned}
$$

(i) If $\tau \leq 1 - S(t)$, then by the consistency of $\hat{S}(t)$, $P(B_n) \to 0$. For any $\epsilon > 0$,

$$
\begin{aligned}
P(|\hat{Q}_Y(\tau \mid t) - 0| > \epsilon) &= P(|\hat{Q}_Y(\tau \mid t)| > \epsilon) \\
&\leq P(|\hat{Q}_Y(\tau \mid t)| > \epsilon, A_n) + P(B_n) \\
&= P(B_n) \to 0.
\end{aligned}
$$

(ii) If $\tau > 1 - S(t)$, we use the convexity lemma (Pollard, 1991) and the quadratic approximation to show the consistency. Recall that the original loss function is $L_\tau(t) = \sum_i \rho_{\tau^*}(Y_i - a - b(T_i - t))K_{h_n}(t - T_i)$ and its practical counterpart $\tilde{L}_\tau(t) = \sum_i \rho_{\hat{\tau}^*}(Y_i - a - b(T_i - t))K_{h_n}(t - T_i)$. Define $m_{\tau^*}(t) = \arg\min_a E(\rho_{\tau^*}(Y - a) \mid T = t)$.

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We first consider the consistency at the left boundary. Let $t_n = ch_n$, where $c$ is a constant. Denote $a_n^* = m_{\tau^*}(t_n)$, $b_n^* = m'_{\tau^*}(t_n)$ and the estimator $\hat{a} = \hat{m}_{\hat{\tau}^*}(t_n)$ and $(\hat{a}, \hat{b})$ minimize $\tilde{L}_\tau(t_n)$. Now, we show the consistency of $\hat{a}$. Denote $Z_i = (1, (T_i - t_n)/h_n)^\top$, $Y_i^* = Y_i - m_{\tau^*}(t_n) - m'_{\tau^*}(t_n)(T_i - t_n)$ and $K_i = K_{h_n}(t_n - T_i)$, $G_n(\theta) = \sum_{i=1}^n \{\rho_{\hat{\tau}^*}(Y_i^* - \theta^\top Z_i/\sqrt{nh_n}) - \rho_{\hat{\tau}^*}(Y_i^*)\}K_i$. Then, $\bar{\theta} = \sqrt{nh_n}(\hat{a} - m_{\tau^*}(t), h_n(\hat{b} - m'_{\tau^*}(t)))^\top$ minimize the function $G_n(\theta)$. For the convex function $G_n(\theta)$, based on the convexity lemma of Pollard (1991), the pointwise convergence of $G_n(\theta)$ to its expectation is sufficient to show the uniform convergence on any compact set of $\theta$. We write $G_n(\theta)$ in the following form

$$G_n(\theta) = E\{G_n(\theta \mid t)\} + (nh_n)^{-1/2}\left(\sum_i \rho'_{\hat{\tau}^*}(Y_i^*)Z_iK_i - E(\rho'_{\hat{\tau}^*}(Y_i^*) \mid T_i)Z_iK_i\right)^\top \theta + R_n(\theta).$$

Let $[-M, M]$ be a interval contains the support of $K$, where $M$ is a real number. Then by Taylor expansion, for $|T_i - t_n| \leq Mh_n$,

$$m_{\tau^*}(T_i) = m_{\tau^*}(t_n) + m'_{\tau^*}(T_i - t_n) + (1/2)m''_{\tau^*}(t_n)(T_i - t)^2 + \xi_{n,i},$$

where $\max_{\{i:|T_i-t_n|\le Mh_n\}} \|\xi_{n,i}\|_\infty = o(h_n^2)$. Then,

$$\begin{aligned}
& E(G_n(\theta) \mid t) \\
= & \sum_i \left[\varphi\left\{m_{\tau^*}(T_i) - a_n - b_n(T_i - t_n) - \frac{\theta^\top Z_i}{nh_n} \mid T_i\right\} - \varphi\{m_{\tau^*}(T_i) - a_n - b_n(T_i - t_n) \mid T_i\}\right] K_i \\
= & \sum_i \varphi'\{m_{\tau^*}(T_i) - a_n - b_n(T_i - t_n) \mid T_i\} \frac{\theta^\top Z_i}{\sqrt{nh_n}} K_i \\
& + \frac{1}{2} \sum_i \varphi''(m_{\tau^*}(T_i) - a_n - b_n(T_i - t_n) \mid T_i) \frac{(\theta^\top Z_i)^2}{nh_n} K_i(1 + o_P(1)) \\
= & \frac{1}{\sqrt{nh_n}} \sum_i E\{\rho'_{\hat{\tau}^*}(Y_i^* \mid T_i)\}(\theta^\top Z_i) K_i + \frac{1}{2nh_n} \theta^\top \left(\sum_i K_i \varphi''(0 \mid T_i) Z_i Z_i^\top\right) \theta(1 + o_P(1)).
\end{aligned}$$

Using (Fan et al., 1994, Lemma 1) and dominated convergence theorem, we have

$$\frac{1}{nh_n} \sum_i K_i \varphi''(0 \mid t_i) Z_i Z_i^\top = H + o_P(1),$$

where $H = \varphi''(0 \mid 0) f(0) \begin{pmatrix} c_0 & c_1 \\ c_1 & c_2 \end{pmatrix}$, and $c_j = \int_{-\infty}^{c} v^j K(v) dv, j = 0, 1, 2$.

Now we show that $R_n(\theta) = o_P(1)$. Recall that

$$R_n(\theta) = G_n(\theta) - E(G_n(\theta) \mid t) - (nh_n)^{-1/2} \left(\sum_i \rho'_{\hat{\tau}^*}(Y_i^*) Z_i K_i - E(\rho'_{\hat{\tau}^*}(Y_i^*) \mid T_i) Z_i K_i\right)^\top \theta$$

Given Conditions (A), we have

$$
\begin{aligned}
E[R_n^2(\theta)] &\leq nE\left\{\rho_{\hat{\tau}^*}(Y_1^* - \theta^\top Z_1/\sqrt{nh_n}) - \rho_{\hat{\tau}^*}(Y_1^*) - \rho'_{\hat{\tau}^*}(Y_1^*)\theta^\top Z_1/\sqrt{nh_n}\right\}^2 K_1^2 \\
&\leq n\int\int\left\{\rho_{\hat{\tau}^*}(Y_1^* - \theta^\top Z_1/\sqrt{nh_n}) - \rho_{\hat{\tau}^*}(Y_1^*) - \rho'_{\hat{\tau}^*}(Y_1^*)\theta^\top Z_1/\sqrt{nh_n}\right\}^2 G(y)d\mu(y) \\
&\quad \times K_{h_n}^2(t_n - \nu)f(\nu)d\nu \\
&= o\left(n\int\frac{(\theta^\top Z_1)^2}{nh_n}K_{h_n}^2(t_n - \nu)f(\nu)d\nu\right) \\
&= o(1).
\end{aligned}
$$

This implies that $R_n(\theta) = o_P(1)$. Thus, we have

$$
G_n(\theta) = (1/2)\theta^\top H\theta + W_n^\top\theta + r_n(\theta),
$$

where $W_n = (nh_n)^{-1/2}\sum_i \rho'_{\hat{\tau}^*}(Y_i^*)Z_iK_i$. As in Fan et al. (1994), we write the quantile loss function $\rho(\cdot)_\tau$ as $\rho_\tau(z) = |z| + (2\tau - 1)z$. Thus, $\rho'_\tau(z) = 1_{z>0} - 1_{z<0} + 2p - 1$ and $\rho''_\tau(z) = 2\delta(z)$, where $\delta(\cdot)$ satisfies $\delta(0) = \infty, \delta(z) = 0, z \neq 0, \int_{-\infty}^{\infty}\delta(z)dz = 1$. In addition, we have $\sup_{\theta\in K}|r_n(\theta)| = o_P(1)$ for any compact set $K$ (Pollard, 1991). Hence, $G_n(\theta)$ can be rewritten as

$$
G_n(\theta) = (1/2)\theta^\top H\theta + W_n^\top\theta + o_P(1). \tag{S4.1}
$$

Thus, we conclude that the convex function $G_n(\theta) - W_n^\top\theta$ converge in probability to $(1/2)\theta^\top H\theta$. Therefore, $\bar{\theta}$, which minimizes $G_n(\theta)$, converges in probability to the minimizer $\hat{\theta}_n = -H^{-1}W_n$. That is,

$$\bar{\theta}_n - \hat{\theta}_n = \sqrt{nh_n}\begin{pmatrix} \hat{a} - m_{\tau^*}(t_n) \\ \\ h_n(\hat{b} - m'_{\tau^*}(t_n)) \end{pmatrix} + \frac{\sum_i \rho'_{\hat{\tau}^*}(Y_i^*)\begin{pmatrix} c_2 - c_1 \frac{T_i - t_n}{h_n} \\ \\ -c_1 + c_0 \frac{T_i - t_n}{h_n} \end{pmatrix} K_i}{\sqrt{nh_n}\{\varphi''(0 \mid 0) f(0)(c_0 c_2 - c_1^2)\}} = o_P(1).$$

The first element of the above equation is

$$\sqrt{nh_n}(\hat{m}_{\hat{\tau}^*}(t_n) - m_{\tau^*}(t_n) - V_n) = o_P(1);$$

$$V_n = \{\varphi''(0 \mid 0) f(0)(c_0 c_2 - c_1^2)\}^{-1} U_n,$$

$$U_n = \frac{1}{nh_n} \sum_i \rho'_{\hat{\tau}^*}(Y_i^*)\{c_2 - c_1(T_i - t_n)/h_n\} K_i.$$

This implies that

$$P(\sqrt{nh_n}|\hat{m}_{\hat{\tau}^*}(t_n) - m_{\tau^*}(t_n) - V_n| \geq \epsilon \mid t) = o_P(1). \tag{S4.2}$$

By Taylor expansion, we have $\varphi'(x \mid t) = \varphi'(0 \mid t) + \varphi''(0 \mid t)x(1 +$

$o(x))$, as $x \to 0$, where

$$\begin{aligned}
\varphi'_{\hat{\tau}^*}(0 \mid T=t) &= E[\rho'_{\hat{\tau}^*}(Y - m_{\tau^*}(t_0) \mid T=t)] \\
&= E(1_{\{Y-m_{\tau^*}(t)>0\}} - 1_{\{Y-m_{\tau^*}(t)<0\}} + 2\hat{\tau}^* - 1) \\
&= (2\hat{\tau}^* - 2)\int_{y<m_{\tau^*}(t)} f(y \mid t)dy + 2\hat{\tau}^* \int_{y>m_{\tau^*}} f(y \mid t)dy \\
&= 2(\hat{\tau}^* - 1)F(m_{\tau^*}(t) \mid t) + 2\hat{\tau}^*[1 - F(m_{\tau^*}(t) \mid t)] \\
&= 2(\hat{\tau}^* - 1)\tau^* + 2\hat{\tau}^*(1-\tau^*) \\
&= 2(\hat{\tau}^* - \tau^*) \\
&= 2\left(\frac{\tau - \{1-\hat{S}(t)\}}{\hat{S}(t)} - \frac{\tau - \{1-S(t)\}}{S(t)}\right)
\end{aligned}$$

Then,

$$\begin{aligned}
U_n &= \frac{1}{nh_n}\sum_i \rho'_{\hat{\tau}^*}(Y_i^*)\{c_2 - c_1(T_i - t_n)/h_n\}K_i \\
&= \frac{1}{nh_n}\sum_i \rho'_{\hat{\tau}^*}(Y_i - a_n - b_n(T_i - t_n))\{c_2 - c_1(T_i - t_n)/h_n\}K_{h_n}(T_n - t_i) \\
&= \frac{1}{nh_n}\sum_i \rho'_{\hat{\tau}^*}\{Y_i - m_{\tau^*}(T_i) + (1/2)m''_{\tau^*}(t_n)(T_i - t_n)^2 + \xi_{n,i}\} \\
&\quad \times\{c_2 - c_1(T_i - t_n)/h_n\}K_{h_n}(T_i - t_n).
\end{aligned}$$

This leads to

$$\begin{aligned}
E(U_n) &= h_n^{-1} E[\varphi'_{\tau^*}\{(1/2)m''_{\tau^*}(t_n)(t-t_n)^2(1+o(1)) \mid t\}\{c_2 - c_1(t-t_n)/h_n\}K_{h_n}(t-t_n)] \\
&= h_n^{-1} E[\{2(\hat{\tau}^* - \tau^*) + \varphi''_{\hat{\tau}^*}(0 \mid t)(1/2)m''_{\tau^*}(t_n)(t-t_n)^2(1+o(1))\} \\
&\quad \times\{c_2 - c_1(t-t_n)/h_n\}K_{h_n}(t_n - t)] \\
&= h_n^{-1}\int_0^1 [\{2(\hat{\tau}^* - \tau^*) + \varphi''_{\hat{\tau}^*}(0 \mid t)(1/2)m''_{\tau^*}(t_n)(t-t_n)^2(1+o(1))\} \\
&\quad \times\{c_2 - c_1(t-t_n)/h_n\}K_{h_n}(t_n - t)]f(t)dt \\
&= \int_{c-1/h_n}^{c} \{2(\hat{\tau}^* - \tau^*) + \varphi''_{\hat{\tau}^*}(0 \mid t)(1/2)m''_{\tau^*}(t_n)h_n^2 v^2(1+o(1))\} \\
&\quad \times(c_2 - c_1 v)K(v)f(x_n - h_n v)dv \\
&= (1/2)m''_{\tau^*}(0)f(0)\varphi''(0 \mid 0)(c_2^2 - c_1c_3)h_n^2(1+o(1)) + o(1) \\
&= dh^2(1+o(1)) + O(\hat{\tau}^* - \tau^*),
\end{aligned}$$

where $d = (1/2)m''_{\tau^*}(0)f(0)\varphi''(0 \mid 0)(c_2^2 - c_1c_3)$. For interior points, key conclusions eq(S4.1)-(S4.2) are still valid with $H = \varphi''(0 \mid t)f(0)\begin{pmatrix} 1 & 0 \\ 0 & \int_{-\infty}^{+\infty} v^2K(v)dv \end{pmatrix}$, $V_n = (\varphi(0 \mid t)f(t)\int_{-\infty}^{+\infty} v^2K(v)dv)^{-1}U_n$ and $U_n = (nh_n)^{-1}\sum_i \rho'_{\hat{\tau}^*}(Y_i^*)K_i\int_{-\infty}^{+\infty} v^2K(v)dv$.

Since $\{c_2 - c_1(T_1 - t_n)/h_n\}K_{h_n}(T_n - t_1)] \le CK_{h_n}(T_n - t_1)]$,

$$
\begin{aligned}
& E[E(U_n \mid t) - E(U_n)]^2 \\
= \;& \frac{1}{nh_n^2} var[\varphi'_{\hat{\tau}^*}(m_{\rho^*}(t_1) - a_n - b_n(t_1 - t_n) \mid t_1)\{c_2 - c_1(t_1 - t_n)/h_n\}K_{h_n}(t_n - t_1)] \\
\leq \;& \frac{c^2}{nh_n^2} E[\varphi'_{\hat{\tau}^*}\left(\frac{1}{2}m''_{\rho^*}(t_n)(t_1 - t_n)^2 + o(h_n^2)\right) K_{h_n}(t_n - t_1)]^2 \\
= \;& \frac{c^2}{nh_n^2} E[\{\varphi'_{\hat{\tau}^*}(0 \mid t_1) + \frac{1}{2}\varphi''_{\hat{\tau}^*}(0 \mid t_1)(m''_{\rho^*}(t_n)(t_1 - t_n)^2 + o(h_n^2))\}K_{h_n}(t_1 - t_n)]^2 \\
= \;& \frac{c^2}{nh_n} \int_{c-\frac{1}{h_n}}^{c} \{2(\hat{\tau}^* - \tau^*) + \varphi''_{\hat{\tau}^*}(0 \mid t_n - h_n v)O(h_n^2)\}^2 K^2(v) f(t_n - h_n v) dv \\
= \;& O\left(\frac{h_n^4}{nh_n}\right) + O\left(\frac{(\hat{\tau}^* - \tau^*)^2}{nh_n}\right) + O\left(\frac{h_n}{n}(\hat{\tau}^* - \tau^*)\right),
\end{aligned}
$$

where the last equality is according to the dominated convergence theorem.

Since $\hat{\tau}^* - \tau^* = o_p(1)$and $P(A_n) \to 0$ for $\tau > 1 - S(t)$, $P(B_n) \to 1$, we have

$$
\begin{aligned}
& P(|\hat{Q}_Y(\tau \mid t_n) - Q_Y(\tau \mid t_n)| > \epsilon \mid t) \\
\leq \;& P(A_n) + P\{|\hat{m}_{\hat{\tau}^*}(t_n) - m_{\tau^*}(t_n)| > \epsilon \mid t\} \\
= \;& P(A_n) + P\{|\hat{m}_{\hat{\tau}^*}(t_n) - m_{\tau^*}(t_n) - V_n| + |V_n| > \epsilon \mid t\} \\
\leq \;& o_p(1) + d^* h_n^2 \{1 + o_p(1)\} \\
\to \;& 0 \text{ (when } h_n \to 0),
\end{aligned}
$$

where $d^* = (1/2)m''_{\tau^*}(0)(c_2^2 - c_1 c_3)/(c_0 c_2 - c_1^2)$.

$$
\begin{aligned}
& P(|\hat{Q}_Y(\tau \mid t_n) - Q_Y(\tau \mid t_n)| > \epsilon) \\
= \;& E[P(|\hat{Q}_Y(\tau \mid t_n) - Q_Y(\tau \mid t_n)| > \epsilon \mid t)] \\
= \;& \int P(|\hat{Q}_Y(\tau \mid t_n) - Q_Y(\tau \mid t_n)| > \epsilon \mid t) d\mu(t) \\
\leq \;& \int_{\{t: P(|\hat{Q}_Y(\tau|t_n) - Q_Y(\tau|t_n)| > \epsilon | t) \leq \epsilon_1\}} \epsilon_1 d\mu(t) \\
& + \int_{\{t: P(|\hat{Q}_Y(\tau|t_n) - Q_Y(\tau|t_n)| > \epsilon | t) > \epsilon_1\}} P(|\hat{Q}_Y(\tau \mid t_n) - Q_Y(\tau \mid t_n)| > \epsilon \mid t) d\mu(t) \\
\leq \;& \epsilon_1 + \int_{\{t: P(|\hat{Q}_Y(\tau|t_n) - Q_Y(\tau|t_n)| > \epsilon | t) > \epsilon_1\}} 1 d\mu(t)
\end{aligned}
$$

With a fixed $\epsilon_1$,

$$
\lim_{n \to \infty} \int_{\{t: P(|\hat{Q}_Y(\tau|t_n) - Q_Y(\tau|t_n)| > \epsilon | t) > \epsilon_1\}} 1 d\mu(t) \to 0.
$$

Then, let $\epsilon_1 \to 0$, $P(|\hat{Q}_Y(\tau \mid t_n) - Q_Y(\tau \mid t_n)| > \epsilon) \to 0$. Hence, we conclude the proof. $\square$

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