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Web-based Supplementary Materials for 'Survival analysis with error-prone time-varying covariates: a risk set calibration approach' by Xiaomei Liao, David Zucker, Yi Li and Donna Spiegelman

Web Appendix A. Some details for the simulation study in Section 6

Web Appendix A.1 *Preliminary simulations for time-invariant exposures*

We considered a conditional normal error model with a time-invariant covariate, with key parameters motivated by the Health Professionals' Follow-up Study (HPFS) as considered in Section 7. In this model, we first generated the true exposure $c \sim N(\mathrm{E}(c), \mathrm{Var}(c))$ with $\mathrm{E}(c) = 0.45$, $\mathrm{Var}(c) = 0.0225$ as in HPFS. The surrogate exposure C has $\mathrm{E}(C) = 0.5$, $\mathrm{Var}(C) = 0.04$. Define $\omega = \mathrm{Var}(C)/\mathrm{Var}(c)$. For each c, we generated the surrogate exposure C from the conditional distribution $C|c$, which also had a normal distribution with conditional mean $\mathrm{E}(C|c) = \alpha + \xi c$ and variance $\mathrm{Var}(C|c) = \omega(1-\rho^2)\mathrm{Var}(c)$, where $\rho = \mathrm{Corr}(c, C)$, which we allowed to vary as 0.3, 0.6, 0.9, $\xi = \rho\sqrt{\omega}$ and $\alpha = \mathrm{E}(C) - \xi\mathrm{E}(c)$.

The survival time T^0 was generated by $T^0 = \frac{1}{\nu}(-e^{-\beta c}\log(1-U_1))^{1/\theta}$ with $U_1 \sim U(0,1)$. Then, the follow-up time, $T = \min(T^0, V, t^*)$, for $t^* = 50$ and V is the censoring time assuming to be exponential with a rate of 1% per year. And, the event indicator, $D = I(T^0 \leqslant \min(V, t^*))$.

The simulation results are given in Web Table 1. We found equally good performance of the ORC and RRC methods with $\mathrm{Var}(c) = 0.0225$. When we increased $\mathrm{Var}(c)$ to be greater than 1, for example, as shown in lower part of Web Table 1, with the means chosen as previously, but with $\mathrm{Var}(c) = 1.0$ and $\mathrm{Var}(C) = 2.0$, then the results indicated a clear advantage of the RRC method over the ORC method, especially in the common disease situation. Additional simulations demonstrated that this advantage became even greater when $\mathrm{Var}(c)$ got even bigger (data not shown).

Web Figure 1 shows the percent change in the regression slope $\hat{\alpha}_1(t)$ as a function of the failure time t, where the percent change of $\hat{\alpha}_1(t)$ is with respect to the value of $\hat{\alpha}_1$ from the ORC method, and is defined as $100 * [\hat{\alpha}_1(t) - \hat{\alpha}_1]/\hat{\alpha}_1$. We fitted a lowess smoother to the data from 1000 simulations. We can see from Web Figure 1 that, with a relatively big variance,

i.e. $\text{Var}(c) = 1$ in the conditional normal error model, there was a big change of $\hat{\alpha}_1(t)$ with respect to the baseline value of $\hat{\alpha}_1$ estimated by ORC when the disease was common, while the change was much smaller when the disease was rare. However, with a small variance, i.e. $\text{Var}(c) = 0.0225$, the changes in $\hat{\alpha}_1(t)$ over time were both very small no matter whether the disease was common or rare. This exactly explained why the RRC estimates were superior in the scenario with big $\text{Var}(c)$, especially in the common disease situation, and agreed with the results presented in Web Table 1.

[Web Table 1 about here.]

[Web Figure 1 about here.]

Web Appendix A.2 *Simulation of survival data for time-varying exposures*

The following is the way to generate the survival time T^0 for cumulatively updated average exposure $x(t)$.

The cumulative incidence function for T^0 was

$$F(t|x(t)) = 1 - \exp(-\int_0^t \lambda(s|x(s))\,ds) = 1 - \exp(-\theta\nu^\theta \int_0^t s^{\theta-1}\exp(\beta x(s))\,ds) \quad \text{(A.1)}$$

If $t_k \leqslant t < t_{k+1}$ for some integer k, we next derived the cumulative incidence function for the cumulatively updated average exposure, $x(t)$, which is

$$\begin{aligned} F(t|x(t)) &= 1 - \exp\left\{-\theta\nu^\theta\left(\sum_{i=0}^{k-1}\int_{t_i}^{t_{i+1}} s^{\theta-1}\exp(\beta x(s))\,ds + \int_{t_k}^{t} s^{\theta-1}\exp(\beta x(s))\,ds\right)\right\} \\ &= 1 - \exp\left\{-\theta\nu^\theta\left(\sum_{i=0}^{k-1}\exp(\beta x(t_i))\int_{t_i}^{t_{i+1}} s^{\theta-1}\,ds + \exp(\beta x(t_k))\int_{t_k}^{t} s^{\theta-1}\,ds\right)\right\} \\ &= 1 - \exp\left\{-\nu^\theta\left(\sum_{i=0}^{k-1}\exp(\beta x(t_i))(t_{i+1}^\theta - t_i^\theta) + \exp(\beta x(t_k))(t^\theta - t_k^\theta)\right)\right\} \quad \text{(A.2)} \end{aligned}$$

with $t_0 = 0$, $x(0) = 0$. For each subject i, we generated the censoring time V_i in the same

way as in Web Appendix A.1. Then, for each subject i, we calculated F_{ij} using (A.2) as

$$F_{ij} = 1 - \exp\left\{-\nu^{\theta}\left(\sum_{u=0}^{j-1}\exp(\beta x_i(t_u))(t_{u+1}^{\theta} - t_u^{\theta})\right)\right\}$$

at each observation time t_j, $j = 1, \cdots, p$. After generating $U_i \sim U(0,1)$, if $F_{ij} \leqslant U_i < F_{i,j+1}$, we solved the following equation for t:

$$U_i = 1 - \exp\left\{-\nu^{\theta}\left(\sum_{i=0}^{j-1}\exp(\beta x(t_i))(t_{i+1}^{\theta} - t_i^{\theta}) + \exp(\beta x(t_j))(t^{\theta} - t_j^{\theta})\right)\right\}. \tag{A.3}$$

Then the solution of (A.3) will be the survival time, which is given by

$$T_i^0 = \left\{t_j^{\theta} - \exp(-\beta x(t_j))\left(\nu^{-\theta}\log(1-U_i) + \sum_{i=0}^{j-1}\exp(\beta x(t_i))(t_{i+1}^{\theta} - t_i^{\theta})\right)\right\}^{\frac{1}{\theta}}. \tag{A.4}$$

If $U_i > F_{i,p}$, then we set T_i^0 to be a big constant $M > t^*$. The follow up time $T_i = \min(T_i^0, V_i, t^*)$ and $D_i = I(T_i^0 \leqslant \min(V_i, t^*))$.

Web Appendix A.3 *Simulation results for time-varying exposures*

Web Table 2 presents the complete results for the CS covariance structure using $\rho_{I_{CS}} = 0.3, 0.6, 0.9$ through different scenario. Web Table 3 presents the results for the AR(1) covariance structure using $\rho_{I_{AR}} = 0.938, 0.978, 0.996$, which can be compared with the results in Web Table 2.

[Web Table 2 about here.]

[Web Table 3 about here.]

Web Appendix B. Asymptotic distribution theory for $\hat{\boldsymbol{\beta}}_{RRC}$

Web Appendix B.1 *Approximate consistency of* $\hat{\boldsymbol{\beta}}_{RRC}$

We assume the following regularity conditions:

1. $\sup_{t\in[0,t^*]}\|\hat{\boldsymbol{\alpha}}_0(t) - \boldsymbol{\alpha}_0(t)\| \xrightarrow{p} \mathbf{0}$, $\sup_{t\in[0,t^*]}\|\hat{\boldsymbol{\alpha}}_1(t) - \boldsymbol{\alpha}_1(t)\| \xrightarrow{p} \mathbf{0}$,
   $\sup_{t\in[0,t^*]}\|\hat{\boldsymbol{\alpha}}_2(t) - \boldsymbol{\alpha}_2(t)\| \xrightarrow{p} \mathbf{0}$.
2. $s^{(0)}(\boldsymbol{\beta}, t)$, $\mathbf{s}^{(1)}(\boldsymbol{\beta}, t)$ and $\mathbf{s}^{(2)}(\boldsymbol{\beta}, t)$ are continuous functions of $\boldsymbol{\beta} \in \mathcal{B}$, uniformly in $t \in$

$[0, t^*]$. $s^{(0)}(\boldsymbol{\beta}, t)$, $\mathbf{s}^{(1)}(\boldsymbol{\beta}, t)$ and $\mathbf{s}^{(2)}(\boldsymbol{\beta}, t)$ are bounded on $\mathcal{B} \times [0, t^*]$; $s^{(0)}(\boldsymbol{\beta}, t)$ is bounded away from zero on $\mathcal{B} \times [0, t^*]$.

3. Define

$$\mathbf{S}^{(2)}(\boldsymbol{\beta}, t) = {n_1}^{-1} \sum_{i=1}^{n_1} Y_m(i, t) \begin{pmatrix} \hat{\mathbf{x}}_i(t) \\ \mathbf{Z}_i(t) \end{pmatrix}^{\otimes 2} \exp\{\boldsymbol{\beta}_1' \hat{\mathbf{x}}_i(t) + \boldsymbol{\beta}_2' \mathbf{Z}_i(t)\},$$

then for $j = 0, 1, 2$, $\sup_{t \in [0, t^*], \beta \in \mathcal{B}} \|\mathbf{S}^{(j)}(\boldsymbol{\beta}, t) - \mathbf{s}^{(j)}(\boldsymbol{\beta}, t)\| \xrightarrow{p} \mathbf{0}$. For a vector v, we denote $v^{\otimes 0} = 1$, $v^{\otimes 1} = v$, $v^{\otimes 2} = vv'$.

Denote the left-hand side of equation (6) as $\mathbf{U}(\boldsymbol{\beta})$ and notice that $\mathbf{U}(\boldsymbol{\beta}) = \partial \mathbf{L}(\boldsymbol{\beta}) / \partial \boldsymbol{\beta}$, where $\mathbf{L}(\boldsymbol{\beta})$ is the log-likelihood function with the expression:

$$n_1^{-1} \mathbf{L}(\boldsymbol{\beta}) = n_1^{-1} \sum_{i=1}^{n_1} \int_0^{t^*} [(\boldsymbol{\beta}_1' \hat{\mathbf{x}}_i(t) + \boldsymbol{\beta}_2' \mathbf{Z}_i(t)) - \log\{S^{(0)}(\boldsymbol{\beta}, \hat{\boldsymbol{\psi}}, t)\}] N_i(dt).$$

We can show that, under the regularity condition 1 - 3, $n_1^{-1} \mathbf{L}(\boldsymbol{\beta}) \xrightarrow{P} \mathbf{H}(\boldsymbol{\beta})$ with

$$\mathbf{H}(\boldsymbol{\beta}) = \int_0^{t^*} [\boldsymbol{\beta}' \mathbf{s}^{(1)}(t) - \log\{s^{(0)}(\boldsymbol{\beta}, t)\} s^{(0)}(t)] \, dt$$

for each $\boldsymbol{\beta}$ in its parameter space $\mathcal{B}$, with $s^{(m)}(\boldsymbol{\beta}, t)$ and $s^{(m)}(t)$ defined as follows:

$$s^{(m)}(\boldsymbol{\beta}, t) = \mathrm{E} \left(Y_m(t) \begin{pmatrix} \tilde{\mathbf{x}}_i(\hat{\boldsymbol{\psi}}, t) \\ \mathbf{Z}_i(t) \end{pmatrix}^{\otimes m} \exp\{\boldsymbol{\beta}_1' \tilde{\mathbf{x}}(t) + \boldsymbol{\beta}_2' \mathbf{Z}(t)\} \right),$$

where $\tilde{\mathbf{x}}(t) = \boldsymbol{\alpha}_0(t) + \boldsymbol{\alpha}_1(t) \mathbf{X}(t) + \boldsymbol{\alpha}_2(t) \mathbf{Z}(t)$, and

$$s^{(m)}(t) = \lambda_0(t) \mathrm{E} \left[Y_m(t) \begin{pmatrix} \tilde{\mathbf{x}}_i(\hat{\boldsymbol{\psi}}, t) \\ \mathbf{Z}_i(t) \end{pmatrix}^{\otimes m} \mathrm{E}\left\{ \exp(\boldsymbol{\beta}_{01}' \mathbf{x}(t) + \boldsymbol{\beta}_{02}' \mathbf{Z}(t)) | T \geqslant t, \mathbf{X}(t), \mathbf{Z}(t) \right\} \right],$$

where $m = 0, 1, 2$, $\boldsymbol{\beta}_0 = (\boldsymbol{\beta}_{01}', \boldsymbol{\beta}_{02}')$ is the true value of $\boldsymbol{\beta} = (\boldsymbol{\beta}_1', \boldsymbol{\beta}_2')$.

Then, the first derivative, $\mathbf{h}(\boldsymbol{\beta}) \doteq \partial \mathbf{H}(\boldsymbol{\beta}) / \partial \boldsymbol{\beta}$, is

$$\mathbf{h}(\boldsymbol{\beta}) = \int_0^{t^*} [\mathbf{s}^{(1)}(t) - \{\mathbf{s}^{(1)}(\boldsymbol{\beta}, t) / s^0(\boldsymbol{\beta}, t)\} s^{(0)}(t)] \, dt$$

and the second derivative, $-\mathbf{I}(\boldsymbol{\beta}) \doteq \partial^2 \mathbf{H}(\boldsymbol{\beta})/\partial \boldsymbol{\beta}^2$, is

$$-\mathbf{I}(\boldsymbol{\beta}) = -\int_0^{t^*} \left[\frac{\mathbf{s}^{(2)}(\boldsymbol{\beta}, t)}{\mathbf{s}^{(0)}(\boldsymbol{\beta}, t)} - \left\{ \frac{\mathbf{s}^{(1)}(\boldsymbol{\beta}, t)}{\mathbf{s}^{(0)}(\boldsymbol{\beta}, t)} \right\}^{\otimes 2} \right] s^{(0)}(t)\, dt.$$

We assume $\mathbf{I}(\boldsymbol{\beta})$ is positive definite, then the second derivative is negative definite. Set $\mathbf{h}(\boldsymbol{\beta}^*) = 0$, thus $\mathbf{H}(\boldsymbol{\beta})$ is a concave function with a unique maximum at $\boldsymbol{\beta} = \boldsymbol{\beta}^*$. Since $\hat{\boldsymbol{\beta}}_{RRC}$ maximizes the concave function $n_1^{-1}\mathbf{L}(\boldsymbol{\beta})$, by convex analysis (Andersen and Gill, 1982), we have $\hat{\boldsymbol{\beta}}_{RRC} \xrightarrow{P} \boldsymbol{\beta}^*$.

Web Appendix B.2 *Asymptotic normality of* $\hat{\boldsymbol{\beta}}_{RRC}$

Since the regression coefficients $\boldsymbol{\psi}(t) = (\boldsymbol{\alpha}_0(t), \boldsymbol{\alpha}_1(t), \boldsymbol{\alpha}_2(t))$ are estimated from the validation study, the variability of these estimates needs to be taken into account. We write the score equation (6) as $\mathbf{U}(\boldsymbol{\beta}, \boldsymbol{\psi})$ to indicate explicitly the dependence on $\boldsymbol{\psi}(t)$. Denote the true value of $\boldsymbol{\psi}(t)$ by $\boldsymbol{\psi}_0(t)$, which is now estimated by $\hat{\boldsymbol{\psi}}(t)$. Then, our estimating equation (6) is now $\mathbf{U}(\hat{\boldsymbol{\beta}}_{RRC}, \hat{\boldsymbol{\psi}}) = 0$. Using Taylor's theorem, we can write

$$\mathbf{0} = \mathbf{U}(\hat{\boldsymbol{\beta}}_{RRC}, \hat{\boldsymbol{\psi}}) \approx \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0) + \frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\beta}}(\hat{\boldsymbol{\beta}}_{RRC} - \boldsymbol{\beta}^*) + \frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\psi}}(\hat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0).$$

Then,

$$n_1^{\frac{1}{2}}(\hat{\boldsymbol{\beta}}_{RRC} - \boldsymbol{\beta}^*) \approx \left[-n_1^{-1} \cdot \frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\beta}} \right]^{-1} \cdot n_1^{-\frac{1}{2}} \left[\mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0) + \frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\psi}}(\hat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0) \right].$$

Set

$$\hat{\mathbf{I}}(\boldsymbol{\beta}^*) = -n_1^{-1} \frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\beta}} = n_1^{-1} \sum_{i=1}^{n_1} \int_0^{t^*} \left[\frac{\mathbf{S}^{(2)}(\boldsymbol{\beta}^*, t)}{\mathbf{S}^{(0)}(\boldsymbol{\beta}^*, t)} - \left\{ \frac{\mathbf{S}^{(1)}(\boldsymbol{\beta}^*, t)}{\mathbf{S}^{(0)}(\boldsymbol{\beta}^*, t)} \right\}^{\otimes 2} \right] N_i(dt),$$

then it can be easily verified that $\hat{\mathbf{I}}(\boldsymbol{\beta}^*) \xrightarrow{P} \mathbf{I}(\boldsymbol{\beta}^*)$ by following the proof in Anderson and Gill(1982). The matrix $\hat{\mathbf{I}}(\boldsymbol{\beta}^*)$ can be estimated by $\hat{\mathbf{I}}_{\boldsymbol{\beta}}$ in (12).

Also, it can be shown by following an argument similar to one used in the proof of theorem 2.1 in Lin and Wei (1989), that $n_1^{-\frac{1}{2}}\mathbf{U}(\boldsymbol{\beta}^*)$ is asymptotically equivalent to $n_1^{-\frac{1}{2}} \sum_{i=1}^{n_1} \mathbf{G}_i(\boldsymbol{\beta}^*)$,

where

$$\mathbf{G}_i(\boldsymbol{\beta}^*) = \int_0^{t^*} \left\{ \begin{pmatrix} \hat{\mathbf{x}}_i(t) \\ \mathbf{Z}_i(t) \end{pmatrix} - \frac{\mathbf{s}^{(1)}(\boldsymbol{\beta}^*, t)}{s^{(0)}(\boldsymbol{\beta}^*, t)} \right\} N_i(dt)$$

$$- \int_0^{t^*} \frac{Y_m(i,t)\exp(\boldsymbol{\beta}_1^* \hat{\mathbf{x}}_i(t) + \boldsymbol{\beta}_2^* \mathbf{Z}_i(t))}{s^{(0)}(\boldsymbol{\beta}^*, t)} \left\{ \begin{pmatrix} \hat{\mathbf{x}}_i(t) \\ \mathbf{Z}_i(t) \end{pmatrix} - \frac{\mathbf{s}^{(1)}(\boldsymbol{\beta}^*, t)}{s^{(0)}(\boldsymbol{\beta}^*, t)} \right\} \tilde{F}(dt)$$

with $\tilde{F}(t) = \mathrm{E}(\sum_{i=1}^{n_1} N_i(t)/n_1)$.

So $n_1^{-\frac{1}{2}}\mathbf{U}(\boldsymbol{\beta}^*) \xrightarrow{D} N(\mathbf{0}, \mathbf{M}_1(\boldsymbol{\beta}^*))$ by the multivariate central limit theorem, with $\mathbf{M}_1(\boldsymbol{\beta}^*) = \mathrm{E}(\mathbf{G}_i(\boldsymbol{\beta}^*)^{\otimes 2})$, which can be estimated by $\hat{\mathbf{H}}_{\boldsymbol{\beta}}$ in (13).

To show the asymptotic normality of $\hat{\boldsymbol{\psi}}$, denote the left-hand side of (8) as $\mathbf{U}_{\boldsymbol{\psi}}(\boldsymbol{\psi})$. Then $\mathbf{U}_{\boldsymbol{\psi}}(\hat{\boldsymbol{\psi}}) = \mathbf{0}$. By the Taylor theorem, we have

$$\mathbf{0} = \mathbf{U}_{\boldsymbol{\psi}}(\hat{\boldsymbol{\psi}}) \approx \mathbf{U}_{\boldsymbol{\psi}}(\boldsymbol{\psi}_0) + \frac{\partial \mathbf{U}_{\boldsymbol{\psi}}}{\partial \boldsymbol{\psi}}(\boldsymbol{\psi}_0)(\hat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0),$$

and it follows that

$$n_2^{\frac{1}{2}}(\hat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0) \approx -\left[\frac{1}{n_2}\frac{\partial \mathbf{U}_{\boldsymbol{\psi}}}{\partial \boldsymbol{\psi}}(\boldsymbol{\psi}_0)\right]^{-1} n_2^{-\frac{1}{2}}\mathbf{U}_{\boldsymbol{\psi}}(\boldsymbol{\psi}_0)$$

Hence, similar reasoning shows that $n_2^{\frac{1}{2}}(\hat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0) \xrightarrow{D} N(\mathbf{0}, \mathbf{M}_2(\boldsymbol{\psi}_0))$ and $\mathbf{M}_2(\boldsymbol{\psi}_0)$ can be estimated by $\hat{\mathbf{V}}_{\hat{\boldsymbol{\psi}}}$ in (10).

Therefore, $n_1^{\frac{1}{2}}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}^*)$ is asymptotically normal with zero mean and covariance matrix $V(\boldsymbol{\beta}^*) = \hat{\mathbf{I}}(\boldsymbol{\beta}^*)^{-1}\tilde{\mathbf{M}}(\boldsymbol{\beta}^*)\hat{\mathbf{I}}(\boldsymbol{\beta}^*)^{-1}$, with $\tilde{\mathbf{M}}(\boldsymbol{\beta}^*) = \mathbf{M}_1(\boldsymbol{\beta}^*) + \frac{1}{n_1 n_2}\frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\psi}}\mathbf{M}_2(\boldsymbol{\psi}_0)(\frac{\partial \mathbf{U}(\boldsymbol{\beta}^*, \boldsymbol{\psi}_0)}{\partial \boldsymbol{\psi}})'$. $V(\boldsymbol{\beta}^*)$ can be consistently estimated by $\hat{\mathbf{I}}_{\boldsymbol{\beta}}^{-1}\hat{\mathbf{H}}_{\boldsymbol{\beta},\boldsymbol{\psi}}\hat{\mathbf{I}}_{\boldsymbol{\beta}}^{-1}$ in (11).

References

Andersen, P. K. and Gill, R. D. (1982). Cox's regression model for counting process: a large sample study. *The Annals of Statistics* **10,** 1100 – 1120.

Lin, D. and Wei, L. (1989). The robust inference for the cox proportional hazards model. *Journal of the American Statistical Association* **84,** 1074–1078.

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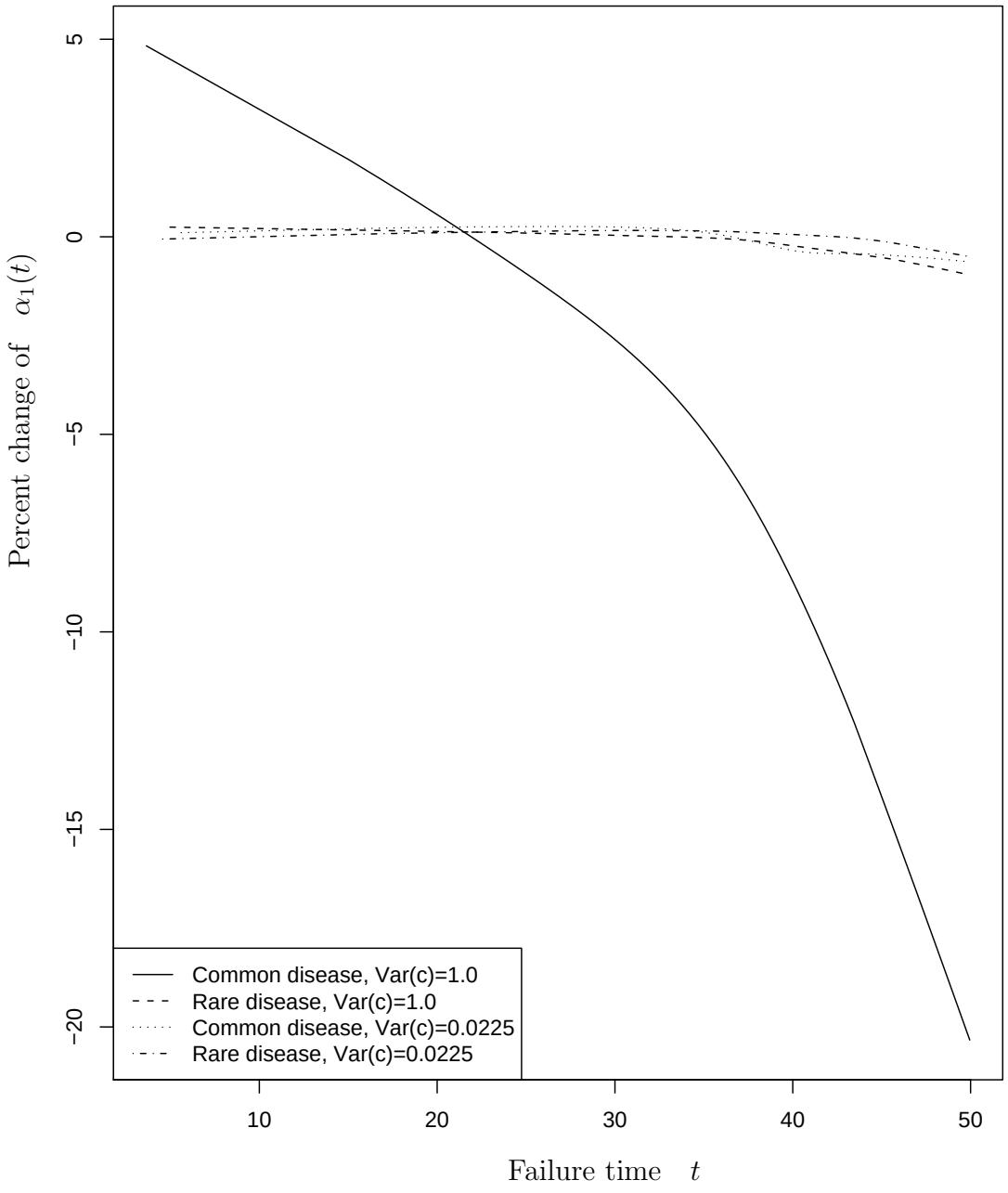

Web Figure 1. Plots were based on $\hat{\alpha}_1(t)$ from the conditional error model simulation with both $\text{Var}(c) = 1.0$ and $\text{Var}(c) = 0.0225$ scenario, $\rho = \text{Corr}(c, C) = 0.3$.

Web Table 1

Results for simulation of time-invariant exposure with a conditional normal error model, for different correlation ρ between c and C.

	Estimated $\hat{\beta}(\hat{SE}[\hat{\beta}])$			Percent Bias(%)			95% CI Coverage(%)		
ρ	Naive	ORC	RRC	Naive	ORC	RRC	Naive	ORC	RRC
	Parameters :	E(c) = 0.45,	Var(c) = 0.0225,	E(C) = 0.5,	Var(C) = 0.04				
	$n_1 = 50000$,	$n_2 = 150$,	Rare disease						
0.3	0.114(0.223)	0.590(1.361)	0.559(1.313)	-77.2	18.0	11.7	59.9	96.9	98.1
0.6	0.226(0.223)	0.509(0.509)	0.512(0.514)	-54.7	1.7	2.4	76.2	95.5	95.4
0.9	0.339(0.223)	0.504(0.333)	0.505(0.333)	-32.2	0.7	1.0	88.7	95.2	94.7
	$n_1 = 50000$,	$n_2 = 500$,	Rare disease						
0.3	0.114(0.223)	0.524(1.029)	0.539(1.052)	-77.2	4.9	7.9	58.1	95.9	96.6
0.6	0.224(0.223)	0.500(0.500)	0.501(0.502)	-55.2	0.0	0.3	75.6	96.4	96.7
0.9	0.335(0.223)	0.497(0.331)	0.497(0.331)	-33.0	-0.6	-0.6	87.7	95.5	95.3
	$n_1 = 1000$,	$n_2 = 150$,	Common disease						
0.3	0.109(0.224)	0.503(1.112)	0.512(1.275)	-78.1	0.6	2.4	58.7	97.6	98.6
0.6	0.230(0.225)	0.520(0.513)	0.523(0.527)	-54.0	4.0	4.6	78.2	95.2	95.9
0.9	0.341(0.225)	0.505(0.334)	0.507(0.336)	-31.7	1.0	1.3	88.9	94.7	95.4
	$n_1 = 1000$,	$n_2 = 500$,	Common disease						
0.3	0.115(0.225)	0.515(1.034)	0.530(1.086)	-77.1	3.1	6.0	59.4	95.7	96.7
0.6	0.227(0.224)	0.508(0.503)	0.509(0.506)	-54.5	1.6	1.7	77.0	95.9	96.0
0.9	0.334(0.225)	0.494(0.333)	0.494(0.334)	-33.3	-1.2	-1.1	88.3	94.7	95.0
	Parameters :	E(c) = 0.45,	Var(c) = 1.0,	E(C) = 0.5,	Var(C) = 2.0				
	$n_1 = 50000$,	$n_2 = 150$,	Rare disease						
0.3	0.107(0.032)	0.557(0.316)	0.566(0.327)	-78.6	11.4	13.2	0.0	94.8	93.8
0.6	0.211(0.032)	0.505(0.095)	0.507(0.103)	-57.7	0.9	1.5	0.0	96.0	95.5
0.9	0.319(0.032)	0.502(0.054)	0.503(0.056)	-36.3	0.4	0.7	0.0	94.5	94.9
	$n_1 = 50000$,	$n_2 = 500$,	Rare disease						
0.3	0.105(0.032)	0.508(0.172)	0.516(0.185)	-79.0	1.6	3.2	0.0	95.8	95.8
0.6	0.212(0.032)	0.501(0.081)	0.503(0.084)	-57.6	0.2	0.6	0.0	95.8	95.8
0.9	0.318(0.032)	0.500(0.051)	0.500(0.052)	-36.5	-0.1	0.0	0.0	95.9	95.6
	$n_1 = 1000$,	$n_2 = 150$,	Common disease						
0.3	0.095(0.032)	0.474(0.220)	0.494(0.276)	-81.1	-5.3	-1.1	0.0	89.1	89.1
0.6	0.198(0.032)	0.473(0.095)	0.506(0.116)	-60.4	-5.3	1.3	0.0	91.6	93.8
0.9	0.311(0.033)	0.490(0.056)	0.500(0.061)	-37.7	-2.1	0.0	0.0	94.6	95.6
	$n_1 = 1000$,	$n_2 = 500$,	Common disease						
0.3	0.095(0.032)	0.457(0.170)	0.506(0.207)	-81.0	-8.6	1.3	0.0	93.6	95.1
0.6	0.198(0.032)	0.468(0.082)	0.500(0.093)	-60.5	-6.4	0.0	0.0	91.3	94.7
0.9	0.310(0.033)	0.487(0.053)	0.497(0.056)	-38.0	-2.6	-0.5	0.0	94.3	95.6

True $\beta = 0.5$, the study duration $t^* = 50$, the number of simulation replications $B = 1000$.
In the rare disease situation, the cumulative incidence is about 1% with $n_1 = 50000$.
In the common disease situation, the cumulative incidence is about 50% with $n_1 = 1000$.

Web Table 2

Results for simulation of cumulatively updated average exposure with a compound symmetry covariance structure, for different intra-class correlation $\rho_{I_{CS}}$.

$\rho_{I_{CS}}$	ρ	Estimated $\hat{\beta}(\hat{SE}[\hat{\beta}])$ Naive	RRC	Percent Bias(%) Naive	RRC	95% CI Coverage(%) Naive	RRC
		$n_1 = 50000$,	$n_2 = 150$,	Rare disease			
0.3	0.3	0.117(0.036)	0.502(0.179)	-76.6	0.4	0.0	95.6
	0.6	0.318(0.058)	0.500(0.098)	-36.3	0.1	12.8	94.1
	0.9	0.464(0.070)	0.499(0.077)	-7.3	-0.3	91.2	95.6
0.6	0.3	0.172(0.032)	0.509(0.118)	-65.6	1.7	0.0	95.0
	0.6	0.373(0.048)	0.498(0.069)	-25.4	-0.4	24.5	95.6
	0.9	0.474(0.054)	0.495(0.057)	-5.1	-0.9	92.6	94.9
0.9	0.3	0.212(0.030)	0.502(0.090)	-57.5	0.3	0.0	94.2
	0.6	0.405(0.041)	0.503(0.056)	-19.1	0.6	37.4	95.0
	0.9	0.486(0.045)	0.501(0.047)	-2.9	0.2	92.8	94.5
		$n_1 = 50000$,	$n_2 = 500$,	Rare disease			
0.3	0.3	0.119(0.036)	0.501(0.157)	-76.2	0.2	0.0	94.5
	0.6	0.313(0.058)	0.489(0.093)	-37.3	-2.1	9.0	95.2
	0.9	0.460(0.070)	0.494(0.076)	-8.0	-1.1	90.8	93.7
0.6	0.3	0.172(0.033)	0.499(0.101)	-65.6	-0.2	0.0	95.0
	0.6	0.374(0.048)	0.499(0.066)	-25.2	-0.2	24.6	95.2
	0.9	0.474(0.054)	0.495(0.057)	-5.2	-0.9	91.6	94.4
0.9	0.3	0.215(0.030)	0.506(0.077)	-57.0	1.2	0.0	94.9
	0.6	0.403(0.041)	0.498(0.052)	-19.5	-0.3	34.2	94.4
	0.9	0.486(0.045)	0.501(0.047)	-2.9	0.2	94.4	95.4
		$n_1 = 1000$,	$n_2 = 150$,	Common disease			
0.3	0.3	0.105(0.035)	0.492(0.193)	-79.1	-1.5	0.0	94.5
	0.6	0.293(0.058)	0.490(0.103)	-41.3	-2.1	4.7	94.4
	0.9	0.438(0.071)	0.490(0.078)	-12.5	-2.0	87.3	95.6
0.6	0.3	0.153(0.033)	0.509(0.135)	-69.4	1.8	0.0	94.1
	0.6	0.352(0.049)	0.503(0.076)	-29.6	0.7	14.3	94.8
	0.9	0.457(0.057)	0.498(0.061)	-8.5	-0.5	88.2	95.1
0.9	0.3	0.185(0.031)	0.502(0.107)	-62.9	0.3	0.0	94.3
	0.6	0.380(0.044)	0.504(0.063)	-24.1	0.8	22.0	94.1
	0.9	0.466(0.049)	0.501(0.052)	-6.8	0.1	89.8	94.6
		$n_1 = 1000$,	$n_2 = 500$,	Common disease			
0.3	0.3	0.103(0.035)	0.483(0.167)	-79.3	-3.3	0.0	94.7
	0.6	0.297(0.058)	0.497(0.096)	-40.7	-0.7	6.1	95.4
	0.9	0.440(0.071)	0.492(0.077)	-12.1	-1.7	86.9	94.7
0.6	0.3	0.152(0.033)	0.498(0.113)	-69.6	-0.4	0.0	93.8
	0.6	0.348(0.049)	0.497(0.071)	-30.5	-0.5	12.5	93.9
	0.9	0.460(0.057)	0.501(0.060)	-8.0	0.1	89.9	95.0
0.9	0.3	0.187(0.031)	0.504(0.089)	-62.5	0.8	0.0	96.2
	0.6	0.378(0.044)	0.503(0.059)	-24.3	0.5	21.8	93.9
	0.9	0.464(0.049)	0.498(0.051)	-7.3	-0.4	88.3	95.5

True $\beta = 0.5$, the study duration $t^* = 50$, the number of simulation replications $B = 1000$.
In the rare disease situation, the cumulative incidence is about 1% with $n_1 = 50000$.
In the common disease situation, the cumulative incidence is about 50% with $n_1 = 1000$.

Web Table 3

Results for simulation of cumulatively updated average exposure with an AR(1) covariance structure, for different intra-class correlation $\rho_{I_{AR}}$.

$\rho_{I_{AR}}$	ρ	Estimated $\hat{\beta}(\hat{SE}[\hat{\beta}])$ Naive	RRC	Percent Bias(%) Naive	RRC	95% CI Coverage(%) Naive	RRC
		$n_1 = 50000$,	$n_2 = 150$,	Rare disease			
0.938	0.3	0.202(0.031)	0.500(0.095)	-59.7	0.0	0.0	95.2
	0.6	0.396(0.043)	0.500(0.059)	-20.9	0.0	30.6	94.6
	0.9	0.482(0.047)	0.499(0.049)	-3.6	-0.3	92.7	94.8
0.978	0.3	0.216(0.030)	0.506(0.089)	-56.7	1.2	0.0	94.2
	0.6	0.405(0.040)	0.498(0.055)	-19.0	-0.5	33.7	95.7
	0.9	0.482(0.044)	0.497(0.046)	-3.6	-0.7	94.3	96.1
0.996	0.3	0.223(0.029)	0.503(0.085)	-55.4	0.7	0.0	94.4
	0.6	0.411(0.039)	0.504(0.053)	-17.8	0.7	39.5	94.6
	0.9	0.486(0.043)	0.501(0.045)	-2.7	0.1	93.2	94.5
		$n_1 = 50000$,	$n_2 = 500$,	Rare disease			
0.938	0.3	0.204(0.031)	0.501(0.081)	-59.2	0.3	0.0	94.5
	0.6	0.392(0.043)	0.492(0.055)	-21.7	-1.6	25.7	94.6
	0.9	0.481(0.047)	0.497(0.049)	-3.8	-0.5	92.1	93.5
0.978	0.3	0.216(0.030)	0.498(0.074)	-56.9	-0.5	0.0	94.5
	0.6	0.405(0.040)	0.499(0.051)	-18.9	-0.1	35.4	94.6
	0.9	0.481(0.044)	0.496(0.046)	-3.8	-0.8	92.4	93.7
0.996	0.3	0.225(0.029)	0.506(0.072)	-55.0	1.2	0.0	95.3
	0.6	0.409(0.039)	0.498(0.049)	-18.3	-0.3	37.1	94.2
	0.9	0.486(0.043)	0.501(0.044)	-2.7	0.1	94.2	95.1
		$n_1 = 1000$,	$n_2 = 150$,	Common disease			
0.938	0.3	0.178(0.031)	0.496(0.109)	-64.5	-0.9	0.0	93.7
	0.6	0.368(0.045)	0.493(0.065)	-26.3	-1.4	17.4	94.8
	0.9	0.460(0.050)	0.495(0.054)	-8.0	-1.0	87.9	96.0
0.978	0.3	0.190(0.031)	0.507(0.105)	-62.0	1.5	0.0	93.5
	0.6	0.382(0.044)	0.502(0.062)	-23.6	0.5	22.1	94.1
	0.9	0.464(0.048)	0.499(0.051)	-7.1	-0.3	88.9	95.4
0.996	0.3	0.194(0.030)	0.501(0.101)	-61.3	0.1	0.0	93.9
	0.6	0.385(0.043)	0.503(0.061)	-22.9	0.7	23.1	94.4
	0.9	0.467(0.047)	0.501(0.050)	-6.6	0.1	89.4	94.3
		$n_1 = 1000$,	$n_2 = 500$,	Common disease			
0.938	0.3	0.176(0.031)	0.489(0.092)	-64.7	-2.2	0.0	94.6
	0.6	0.370(0.045)	0.498(0.060)	-25.9	-0.5	17.4	95.6
	0.9	0.461(0.050)	0.496(0.053)	-7.8	-0.8	88.1	94.4
0.978	0.3	0.189(0.031)	0.497(0.086)	-62.1	-0.6	0.0	94.1
	0.6	0.378(0.044)	0.498(0.057)	-24.4	-0.4	19.9	93.7
	0.9	0.467(0.048)	0.501(0.051)	-6.7	0.2	89.1	94.1
0.996	0.3	0.195(0.030)	0.503(0.084)	-60.9	0.6	0.0	96.3
	0.6	0.384(0.043)	0.502(0.056)	-23.3	0.3	23.4	93.3
	0.9	0.465(0.047)	0.498(0.049)	-7.0	-0.3	88.2	95.3

True $\beta = 0.5$, the study duration $t^* = 50$, the number of simulation replications $B = 1000$.
In the rare disease situation, the cumulative incidence is about 1% with $n_1 = 50000$.
In the common disease situation, the cumulative incidence is about 50% with $n_1 = 1000$.
$\rho_{I_{AR}} = 0.938, 0.978, 0.996$ are respectively in an equal footing with $\rho_{I_{CS}} = 0.3, 0.6, 0.9$ according to the equation (15).