Supplemental material

S1. Full specification of the AUC and PE

Area under the ROC curve

The estimated AUC can be decomposed as

$$\widehat{\mathrm{AUC}}(t, \Delta t) = \widehat{\mathrm{AUC}}_1(t, \Delta t) + \widehat{\mathrm{AUC}}_2(t, \Delta t) + \widehat{\mathrm{AUC}}_3(t, \Delta t) + \widehat{\mathrm{AUC}}_4(t, \Delta t).$$

Here AUC_1 refers to the patients pairs whose survival times can be ordered directly and is given by

$$\widehat{\mathrm{AUC}}_1(t, \Delta t) = \frac{\sum_{i=1}^{n} \sum_{j=1;j\neq i}^{n} I\{\hat{\pi}_i(t + \Delta t \mid t) < \hat{\pi}_j(t + \Delta t \mid t)\} \times I\{\Omega_{ij}^{(1)}(t)\}}{\sum_{i=1}^{n} \sum_{j=1;j\neq i}^{n} I\{\Omega_{ij}^{(1)}(t)\}},$$

with $I(\cdot)$ as the indicator function and

$$\Omega_{ij}^{(1)}(t) = [\{T_i \in (t, t + \Delta t]\} \cap \{\delta_i = 1\} \cap \{S_i = 1\}] \cap [\{T_j > t + \Delta t\} \cap \{S_j = 1\}],$$

indicates that the event times are not censored, both patients belong to the randomly drawn subcohort ($S_i = 1$), $i, j = 1, ..., n$ and $i \neq j$.

$\mathrm{AUC}_2(t, \Delta t)$, $\mathrm{AUC}_3(t, \Delta t)$, $\mathrm{AUC}_4(t, \Delta t)$ refer to the patient pairs where censoring occurs. Their corresponding indicator functions $I\{\Omega_{ij}^{(m)}(t)\}$ are

$$\Omega_{ij}^{(2)}(t) = [\{T_i \in (t, t + \Delta t]\} \cap \{\delta_i = 0\} \cap \{S_i = 1\}] \cap [\{T_j > t + \Delta t\} \cap \{S_j = 1\}],$$

for the pairs where i is a censored patient and j experiences an event,

$$\Omega_{ij}^{(3)}(t) = [\{T_i \in (t, t + \Delta t]\} \cap \{\delta_i = 1\} \cap \{S_i = 1\}] \cap [\{T_i < T_j \leq t + \Delta t\} \cap \{\delta_j = 0\} \cap \{S_j = 1\}],$$

for the pairs where i is a patient that experiences an event and j is censored, and finally

$$\Omega_{ij}^{(4)}(t) = [\{T_i \in (t, t + \Delta t]\} \cap \{\delta_i = 0\} \cap \{S_i = 1\}] \cap [\{T_i < T_j \leq t + \Delta t\} \cap \{\delta_j = 0\} \cap \{S_j = 1\}],$$

for the pairs where both i and j are censored patients.

$\widehat{\mathrm{AUC}}_m(t, \Delta t)$ can be estimated by

$$\widehat{\mathrm{AUC}}_m(t, \Delta t) = \frac{\sum_{i=1}^{n} \sum_{j=1;j\neq i}^{n} I\{\hat{\pi}_i(t + \Delta t \mid t) < \hat{\pi}_j(t + \Delta t \mid t)\} \times I\{\Omega_{ij}^{(m)}(t)\} \times \hat{\nu}_{ij}^{(m)}}{\sum_{i=1}^{n} \sum_{j=1;j\neq i}^{n} I\{\Omega_{ij}^{(m)}(t)\} \times \hat{\nu}_{ij}^{(m)}},$$

with $m = 2, 3, 4$. For the pairs where censoring occurs, we use $\hat{\nu}_{ij}^{(m)}$ as weighting functions for the probability that the patients would have been comparable (i.e. without censoring), with $\hat{\nu}_{ij}^{(2)} = 1 - \hat{\pi}_i(t+\Delta t \mid T_i)$, $\hat{\nu}_{ij}^{(3)} = 1 - \hat{\pi}_j(t+\Delta t \mid T_j)$ and $\hat{\nu}_{ij}^{(4)} = \{1 - \hat{\pi}_i(t+\Delta t \mid T_i)\} \times \hat{\pi}_j(t+\Delta t \mid T_j)$.

Prediction error

The calibration is measured by the prediction error (PE), where low values of PE show a well-calibrated model. The expected prediction error is as follows:

$$\mathrm{PE}(t + \Delta t \mid t) = E[\{I(T_j^* > t + \Delta t) - \pi_j(t + \Delta t \mid t)\}^2].$$

An appropriate estimator for time-to-event data is

$$\begin{aligned}\widehat{\mathrm{PE}}(t + \Delta t \mid t) =& \{n(t)\}^{-1} \sum_{j:T_j \geq t} \Big\{ I(T_j \geq t + \Delta t)\{1 - \hat{\pi}_j(t + \Delta t \mid t)\}^2 \\ & + \delta_j I(T_j < t + \Delta t)\{0 - \hat{\pi}_j(t + \Delta t \mid t)\}^2 + (1 - \delta_j) I(T_j < t + \Delta t) \\ & \times \big[\hat{\pi}_j(t + \Delta t \mid T_j)\{1 - \hat{\pi}_j(t + \Delta t \mid t)\}^2 + \{1 - \hat{\pi}_j(t + \Delta t \mid T_j)\}\{0 - \hat{\pi}_j(t + \Delta t \mid t)\}^2\big] \Big\}.\end{aligned}$$

In this equation $n(t)$ denotes the number of patients still at risk at time t and the remaining parts sum over three types of situations. The first and second terms correspond to the patients that were still event free after $t + \Delta t$ and the patient that experienced the event between t and Δt, respectively. The third term refers to the patients that were censored in the interval $[t, t + \Delta t]$.

S2. Extensive results from the simulation study

Supplemental Table 1. Results from estimating a joint model on simulated data based on 200 replications per scenario.

% Events		Scenario	Size subcohort: 1/3			Scenario	Size subcohort: 1/6		
			FC	CCI	CCII		FC	CCI	CCII
	α		0.975	0.971	0.849		0.976	0.966	0.799
	bias		-0.025	-0.029	-0.151		-0.024	-0.034	-0.201
	(2.5% - 97.5%)		(0.89 - 1.07)	(0.88 - 1.07)	(0.76 - 0.94)		(0.89 - 1.07)	(0.88 - 1.06)	(0.71 - 0.89)
	coverage		92%	91%	13%		92%	88%	4%
	β_1		1.003	0.996	1.087		1.004	0.986	1.139
	bias		0.003	-0.004	0.087		0.004	-0.014	0.139
	(2.5% - 97.5%)		(0.92 - 1.08)	(0.89 - 1.10)	(0.98 - 1.19)		(0.93 - 1.08)	(0.86 - 1.11)	(1.02 - 1.26)
	coverage		93%	92%	62%		97%	96%	36%
	β_2		0.319	0.331	0.558		0.325	0.357	0.713
	bias		0.019	0.031	0.258		0.025	0.057	0.413
	(2.5% - 97.5%)		(0.25 - 0.39)	(0.23 - 0.43)	(0.45 - 0.66)		(0.25 - 0.40)	(0.24 - 0.47)	(0.60 - 0.83)
	coverage		93%	91%	1%		89%	83%	0%
20%	β_3	1	0.110	0.104	0.142	2	0.109	0.097	0.154
	bias		0.01	0.004	0.042		0.009	-0.003	0.054
	(2.5% - 97.5%)		(0.09 - 0.13)	(0.08 - 0.13)	(0.12 - 0.17)		(0.09 - 0.13)	(0.07 - 0.12)	(0.12 - 0.19)
	coverage		82%	94%	12%		84%	98%	8%
	β_4		0.104	0.105	0.092		0.102	0.099	0.092
	bias		0.004	0.005	-0.008		0.002	-0.001	-0.008
	(2.5% - 97.5%)		(0.00 - 0.21)	(-0.04 - 0.25)	(-0.06 - 0.24)		(-0.10 - 0.21)	(-0.07 - 0.27)	(-0.08 - 0.27)
	coverage		95%	93%	92%		96%	93%	96%
	γ		-1.979	-1.987	-1.774		-1.979	-1.978	-1.676
	bias		0.021	0.013	0.226		0.021	0.022	0.324
	(2.5% - 97.5%)		(-2.27 - -1.7)	(-2.29 - -1.7)	(-2.06 - -1.50)		(-2.27 - -1.70)	(-2.28 - -1.68)	(-1.96 - -1.40)
	coverage		95%	94%	65%		93%	95%	42%

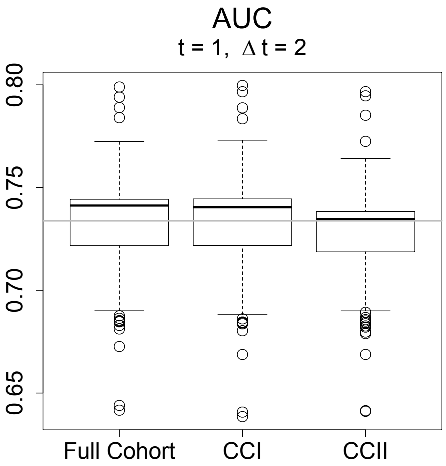
	α		0.856	0.845	0.727		0.858	0.835	0.649
	bias		-0.144	-0.155	-0.273		-0.142	-0.165	-0.351
	(2.5% - 97.5%)		(0.74 - 0.99)	(0.72 - 0.98)	(0.61 - 0.86)		(0.74 - 0.99)	(0.71 - 0.97)	(0.53 - 0.78)
	coverage		38%	33%	1%		39%	32%	0%
	β_1		1.003	0.993	1.062		1.005	0.990	1.127
	bias		0.003	-0.007	0.062		0.005	-0.010	0.127
	(2.5% - 97.5%)		(0.92 - 1.08)	(0.87 - 1.12)	(0.93 - 1.19)		(0.93 - 1.09)	(0.82 - 1.16)	(0.96 - 1.29)
	coverage		96%	95%	82%		96%	90%	64%
	β_2		0.331	0.343	0.474		0.334	0.371	0.638
	bias		0.031	0.042	0.174		0.034	0.071	0.339
	(2.5% - 97.5%)		(0.25 - 0.41)	(0.21 - 0.47)	(0.34 - 0.61)		(0.25 - 0.41)	(0.19 - 0.55)	(0.46 - 0.82)
	coverage		88%	91%	29%		88%	87%	4%
	β_3		0.108	0.099	0.127		0.106	0.087	0.146
5%	bias	3	0.008	-0.001	0.027	4	0.006	-0.013	0.046
	(2.5% - 97.5%)		(0.09 - 0.13)	(0.06 - 0.13)	(0.09 - 0.16)		(0.08 - 0.13)	(0.04 - 0.13)	(0.10 - 0.20)
	coverage		90%	99%	70%		93%	92%	58%
	β_4		0.101	0.103	0.055		0.100	0.107	0.023
	bias		0.001	0.003	-0.045		0.00	0.007	-0.077
	(2.5% - 97.5%)		(-0.01 - 0.21)	(-0.07 - 0.28)	(-0.12 - 0.24)		(-0.01 - 0.21)	(-0.12 - 0.34)	(-0.22 - 0.26)
	coverage		94%	94%	91%		95%	95%	88%
	γ		-2.730	-2.760	-2.421		-2.771	-2.806	-2.238
	bias		-0.73	-0.76	-0.421		-0.771	-0.806	-0.238
	(2.5% - 97.5%)		(-3.36 - -2.15)	(-3.44 - -2.13)	(-3.06 - -1.83)		(-3.40 - -2.18)	(-3.51 - -2.15)	(-2.89 - -1.63)
	coverage		26%	32%	76%		24%	31%	93%

The *bias* indicates the difference between the simulated parameter value and the estimated value by each of the models. The *coverage* is calculated by the percentage of times the true simulated values falls in the credible interval of each simulation.

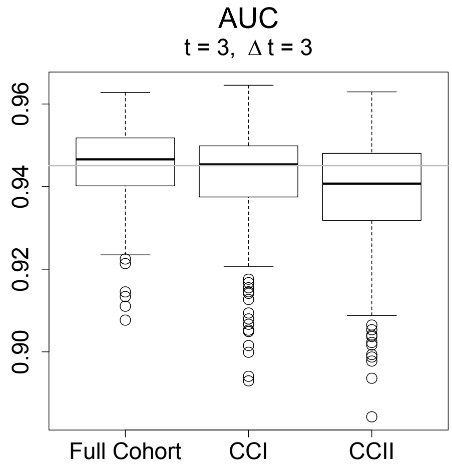
Simulated values of the parameters: α = 1, β_1 = 1, β_2 = 0.3, β_3 = 0.1, β_4 = 0.1, γ = -2.

FC, Full cohort; CCI, Case-cohort design - retain all survival information; CCII: Case-cohort design - classical version

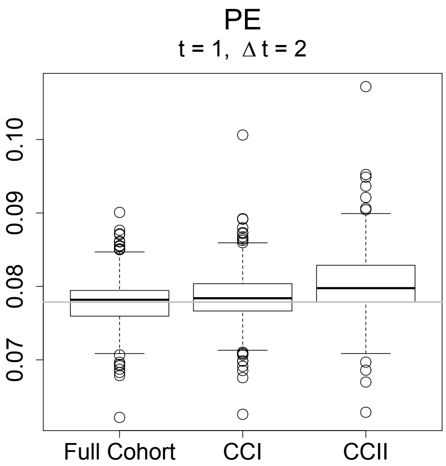
S3. Boxplots for simulation results



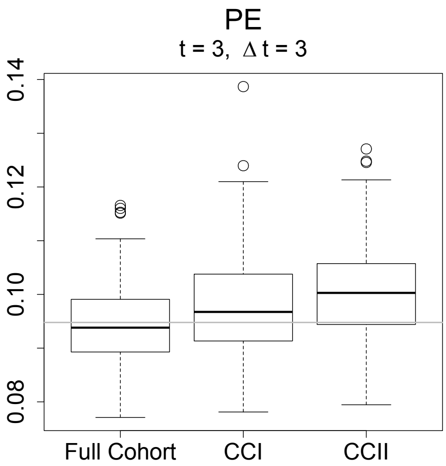
(a)



(b)

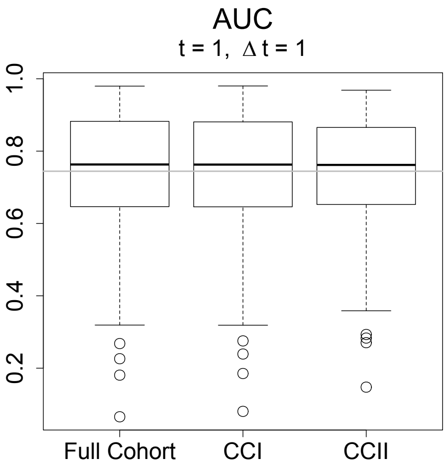


(c)

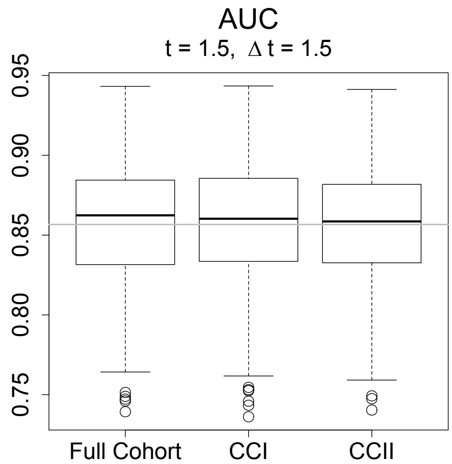


(d)

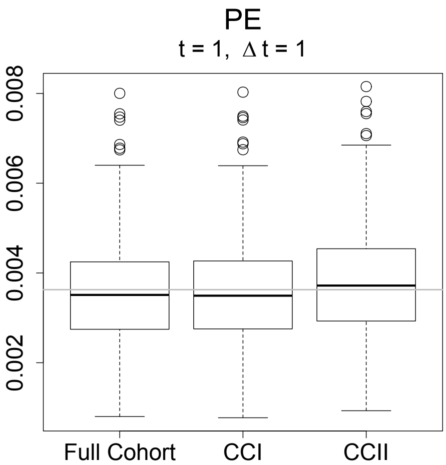
Supplemental Figure 1: Predictive accuracy measures from scenario 1



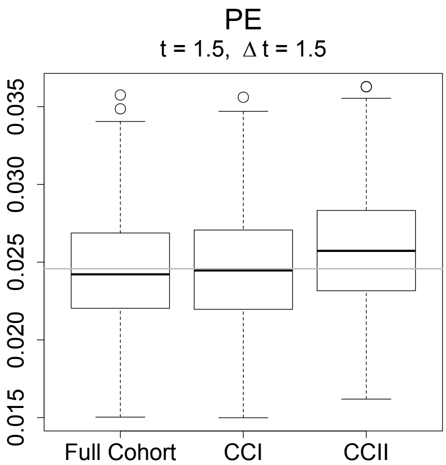
(a)



(b)

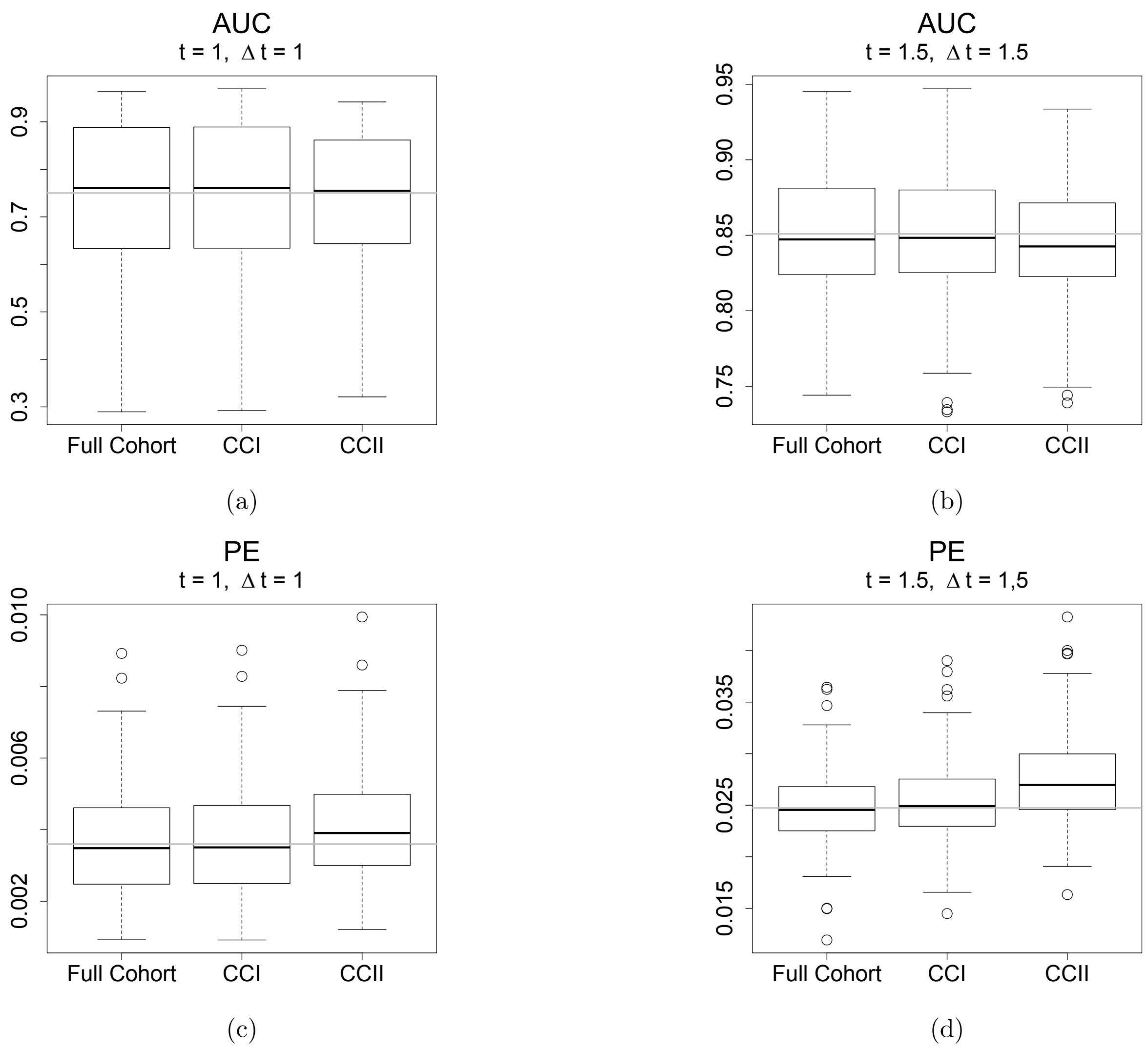


(c)



(d)

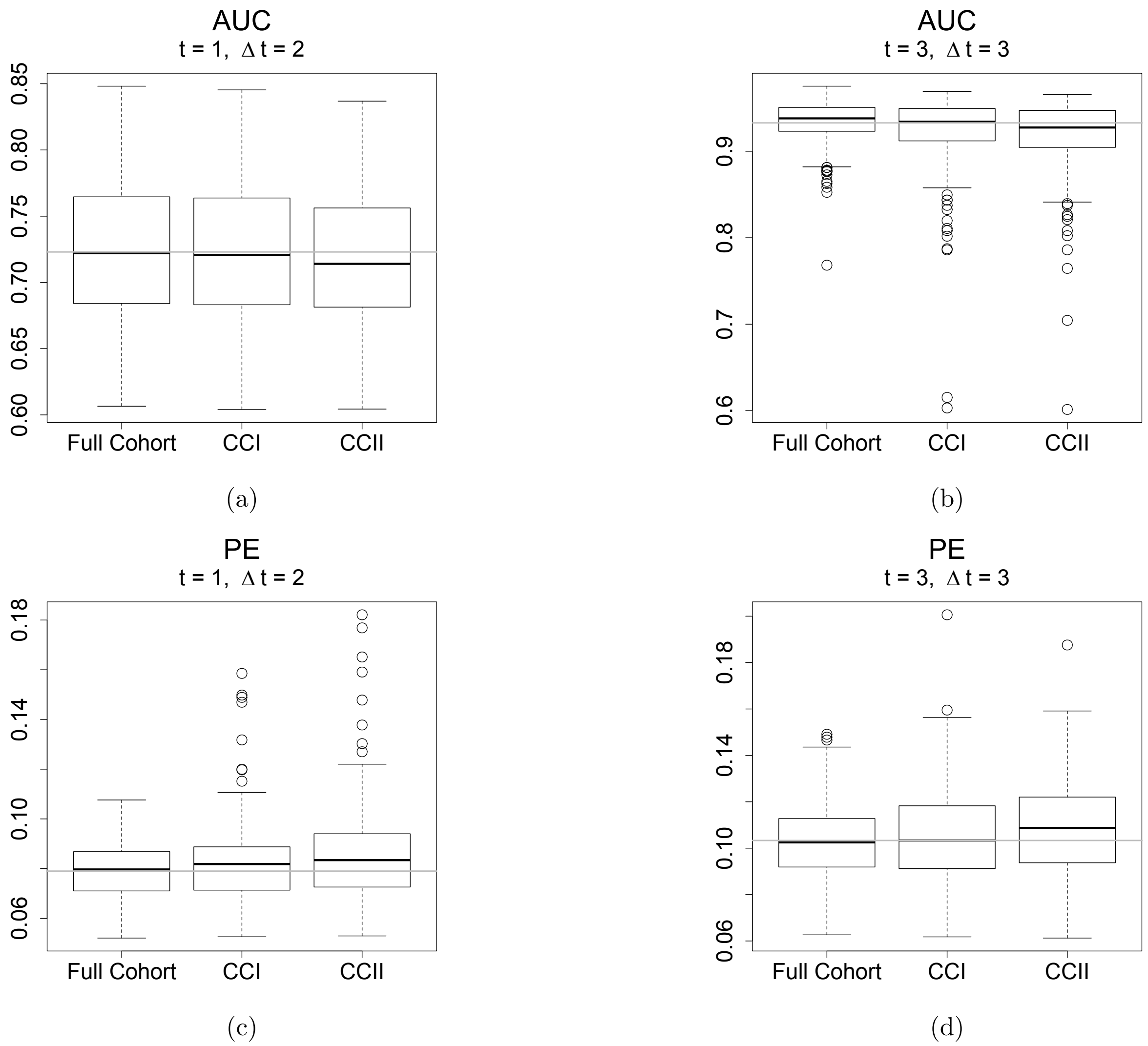
Supplemental Figure 2: Predictive accuracy measures from scenario 3



Supplemental Figure 3: Predictive accuracy measures from scenario 4

S4. Results from a simulation study with 500 simulated subjects.

We have performed an additional simulation study, to evaluate our method in data sets with less subjects. We simulated data sets with 500 subjects, and event rate of 25% and imitated a case-cohort design with a subcohort size of 1/3 of the full cohort. Supplemental table 2 and supplemental figure 4 show the results of this simulation. All results are in line with the previous simulations, where the newly proposed version of the case-cohort performs similar to the full cohort and the standard version of the case-cohort design performs less well. The differences, however are less pronounced in these simulations.



(a) (b) (c) (d)

Supplemental Figure 4: Predictive accuracy measures of estimated joint models on simulated data based on 200 replications per scenario - with n = 500, ER = 25% and size of CC = 1/3

Supplemental Table 2. Results from estimating a joint model on simulated data based on 200 replications per scenario - with n = 500, ER = 25% and size of CC = 1/3

	FC	CCI	CCII
	Summary simulated data		
patients, n	500	500	250
events, n	125	125	125
event rate, %	25%	25%	50%
measurements, n	2500	1350	1350
	Results simulations		
α	0.905	0.894	0.793
bias	-0.095	-0.106	-0.207
(2.5% - 97.5%)	(0.76 - 1.07)	(0.74 - 1.07)	(0.64 - 0.96)
coverage	78%	77%	35%
β_1	1.006	0.982	1.085
bias	0.006	-0.018	0.085
(2.5% - 97.5%)	(0.85 - 1.16)	(0.76 - 1.20)	(0.87 - 1.30)
coverage	92%	92%	89%
β_2	0.305	0.348	0.540
bias	0.005	0.048	0.240
(2.5% - 97.5%)	(0.16 - 0.45)	(0.14 - 0.55)	(0.33 - 0.75)
coverage	96%	92%	38%
β_3	0.115	0.099	0.155
bias	0.015	-0.001	0.055
(2.5% - 97.5%)	(0.08 - 0.15)	(0.05 - 0.15)	(0.10 - 0.22)
coverage	93%	95%	57%
β_4	0.104	0.123	0.108
bias	0.004	0.023	0.008
(2.5% - 97.5%)	(-0.11 - 0.32)	(-0.18 - 0.42)	(-0.20 - 0.41)
coverage	97%	95%	94%
γ_1	-1.920	-1.939	-1.726
bias	0.08	0.061	0.274
(2.5% - 97.5%)	(-2.48 - -1.40)	(-2.53 - -1.38)	(-2.30 - -1.19)
coverage	94%	95%	83%

The *bias* indicates the difference between the simulated parameter value and the estimated value by each of the models. The *coverage* is calculated by the percentage of times the true simulated values falls in the credible interval of each simulation.
Simulated values of the parameters: α = 1, β_1 = 1, β_2 = 0.3, β_3 = 0.1, β_4 = 0.1, γ = -2.
FC, Full cohort; CCI, Case-cohort design - retain all survival information; CCII: Case-cohort design - classical version

S5. Data Sharing

The code for simulating data from the simulation study and performing the analyses can be found at: https://github.com/SaraBaart/JM-CaseCohort

The data from the clinical application that support the findings of this study are available from the corresponding author upon reasonable request.