Time to dementia onset: competing risk analysis with Laplace regression

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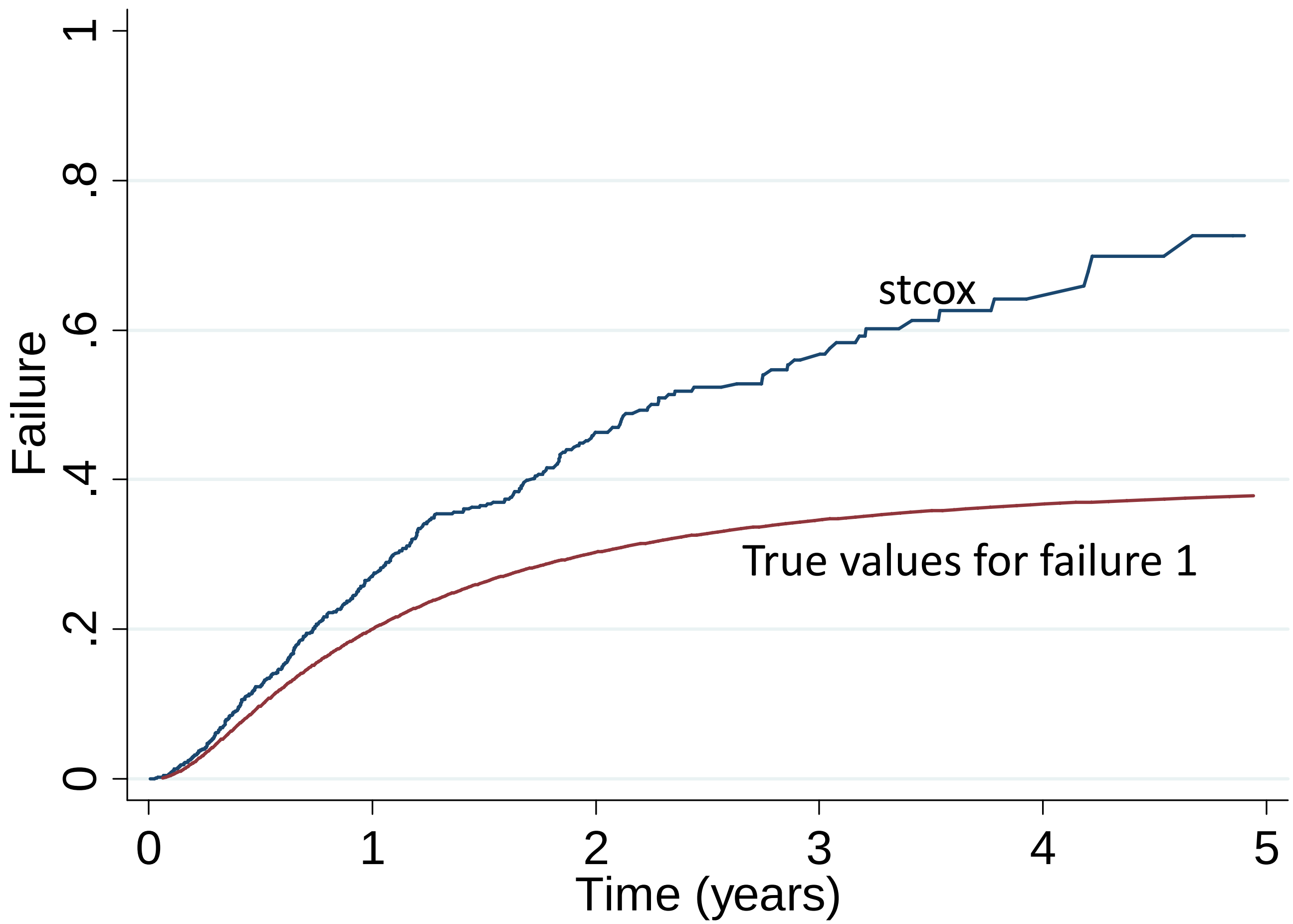
Why competing risks?

Simulation: 1000 subjects
167 subjects (17%) (censored data)
423 subjects (42%) (i.e. dementia onset)
410 subjects (41%) (i.e. all cause of mortality)



Laplace regression

Laplace regression estimates the conditional quantiles of a continuous outcome variable given a set of covariates in the presence of random censoring.

We observe: $Y_i = \min(T_i, C_i) \quad i = 1,2 \ldots N$

The failure is defined as: $\delta_i = I(T_i \leq C_i)$

Assumptions:

conditionally on the covariates, the outcome follows an asymmetric Laplace distribution.

Laplace regression

The coefficients are found by maximizing the likelihood function:

Event — Censored event

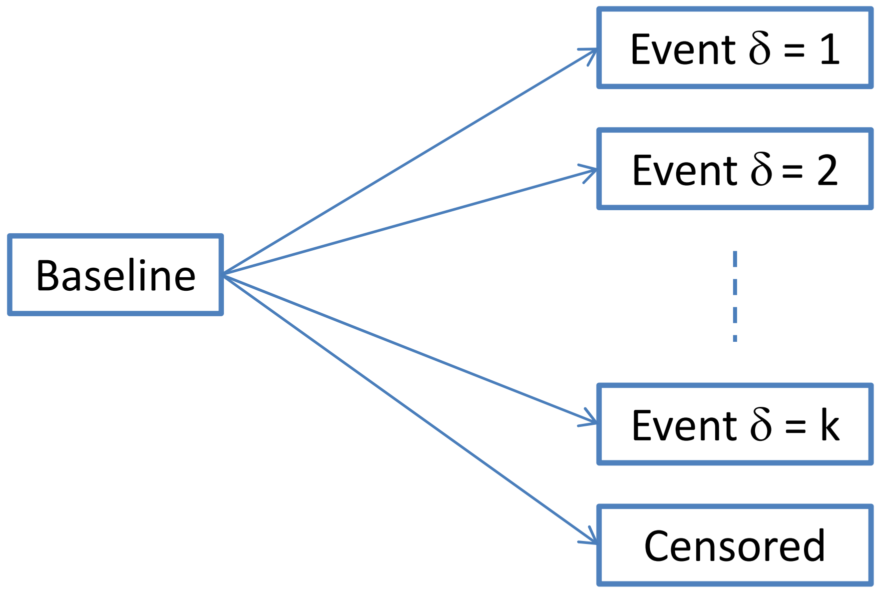
$$l_n = \sum_i \delta_i \log f(y_i \mid x_i) + (1-\delta_i)\log[1 - F(y_i \mid x_i)]$$

- l_n: Probability of the event
- Event term: Probability of event at that moment
- Censored event term: Probability of event after that moment

Note:

1. The censoring can be dependent on the set of covariates ($C_i = f(x_i)$);
2. Laplace regression is a robust regression method;
3. Laplace regression gives the similar results as the Kaplan-Meier when no covariates are introduced.

Competing risks Laplace regression



Suppose δ=j is the event of interest and $\delta \neq$j are the competing events.
T is the time to first event or censoring.
The failure variable is defined as:

$$Failure = \begin{matrix} 0 & \text{censored} \\ 1 & \text{event 1} \\ \vdots & \vdots \\ k & \text{event k} \end{matrix}$$

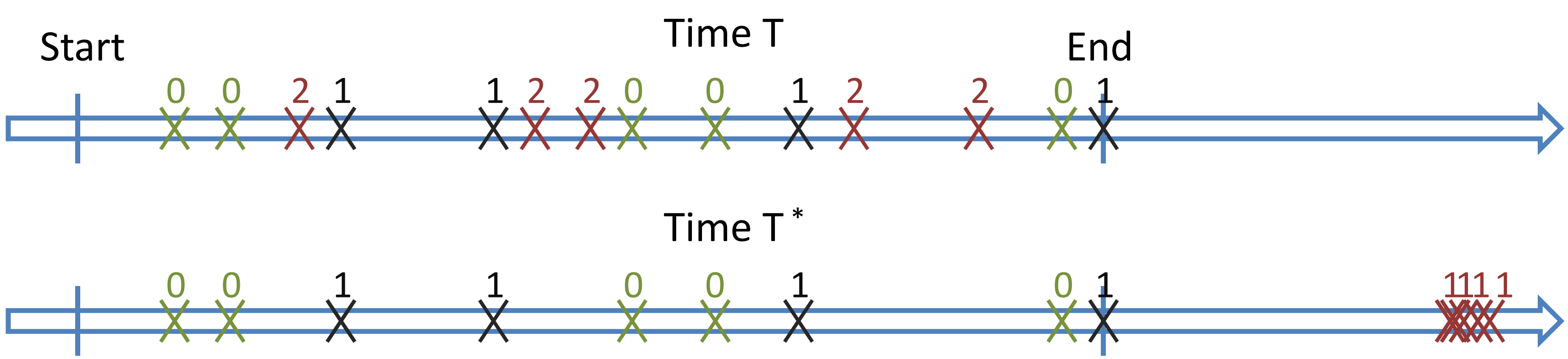
Competing risks Laplace regression

For simplicity, consider two events only: $\delta = 1$ and $\delta = 2$.
Suppose $\delta = 1$ is the event of interest and $\delta = 2$ is the competing event.

We analyze the new time variable defined as: $T^* = T \cdot I(\delta \neq 2) + T_\infty \cdot I(\delta = 2)$

•Elandt-J. *Scandinavian Actuarial Journal* (1976)
•Gray RJ. *Annals of Statistics* (1988)

cause of failure: $Failure^* = \begin{cases} 0 & \text{censored} \\ 1 & \text{event 1 and 2} \end{cases}$



Advantages:

1. No assumption on proportionality of the regression coefficients;
2. Derive directly the cumulative incidence function (CIF) of the failure of interest;
3. Intuitive results;
4. Intuitive concept of competing risks.

Simulation

$$T_1 = e^{2x_1} + N(0,1)$$
$$T_C = e^{-0.5x_1 - 0.5x_2} + N(0,1)$$
$$x_1 \sim Bernoulli(0.5)$$
$$x_2 \sim U(0,1)$$

$$\Pr(\delta = 1 | X) = 0.8I(x_1 = 0) + 0.6I(x_1 = 1)$$

Censored data	27%
Event of interest	52%
Competing event	21%

```
// Generate new time and failure variables

sum time
gen time_new = Time*(failure!=2)+r(max)*2*(failure==2)
gen failure_new = (failure!=0)

// Fit Laplace model

laplace time_new x1 x2, fail(failure_new) q(2(2)80)
```

Simulation

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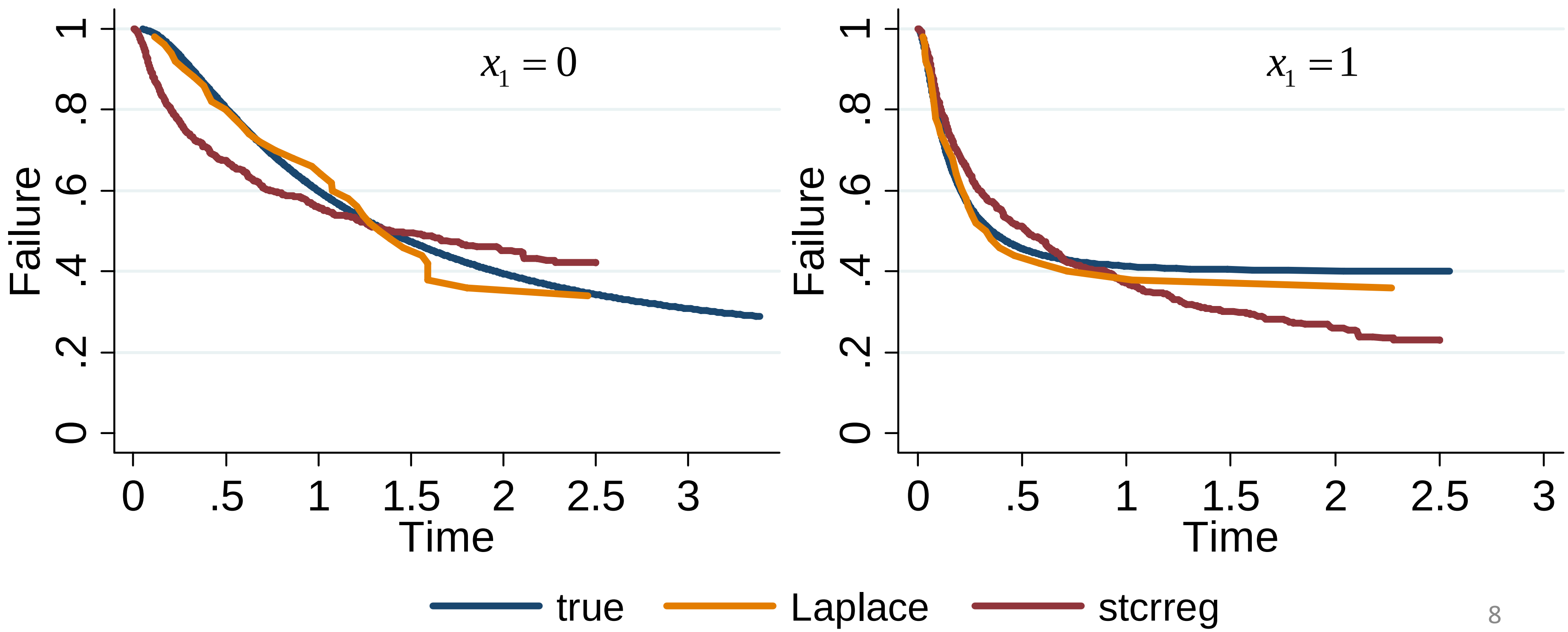
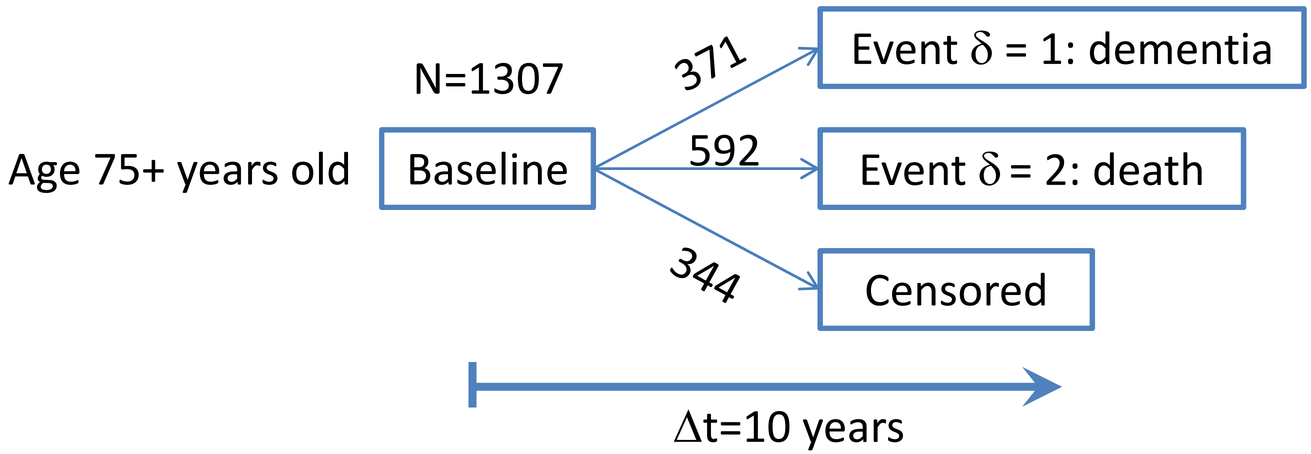


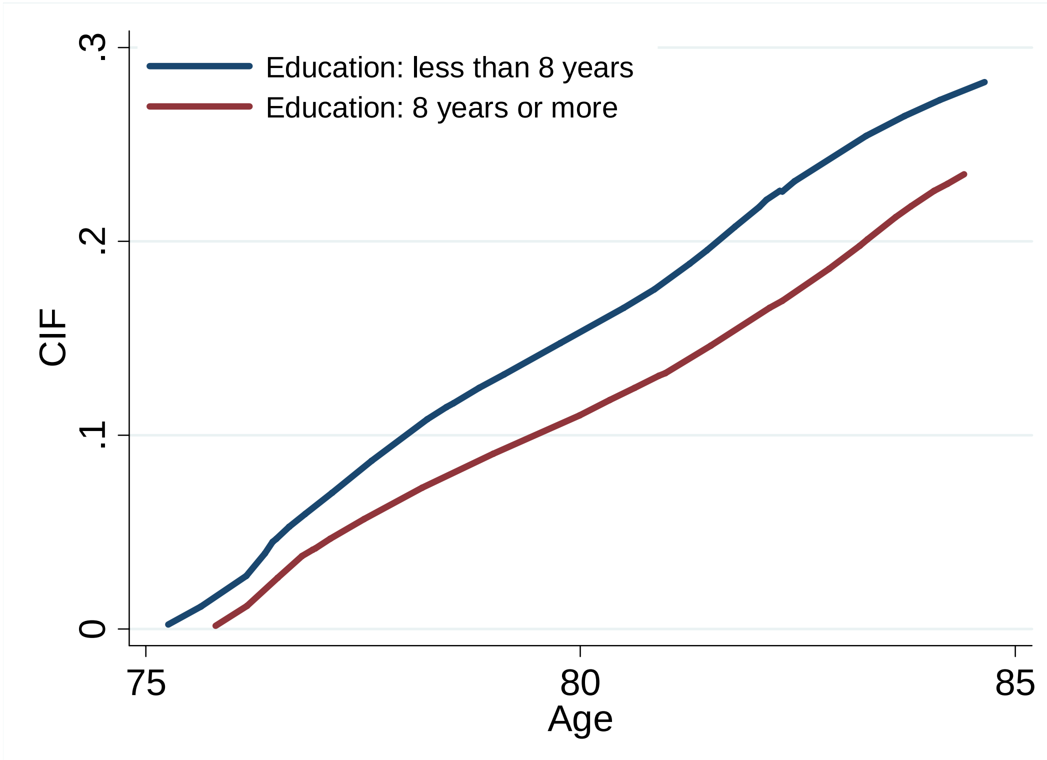
Time to dementia onset



Data from Kungsholmen Project: longitudinal population-based study on ageing and dementia

Event	
Censored data	26%
Dementia	29%
Death	45%

Time to dementia onset




```
laplace time_new education age sex, fail(dementia) q(1 10 15 20)

// Use post-estimation commands to tabulate the results

lincom [q10]_cons+[q10]education

lincom [q10]_cons+[q10]education-[q15]_cons
```

Time to dementia onset

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Education	Percent	Age at dementia	*CI*
<8years	1%	76.6	(76-4, 76.9)
	10%	78.9	(78.1, 79.8)
	15%	80.3	(78.8, 81.7)
	20%	82.3	(81.1, 83.5)
≥8 years	1%	76.9	(76.6, 77.2)
	10%	80.4	(79.7, 81.2)
	15%	82.2	(81.2, 83.1)
	20%	83.9	(83.0, 84.8)

Δt=0.2 years
p-value=.825
CI(-1.2, 1.5)

Percent	*Δt (years)*	*p-value*
1%	0.2	<0.109
10%	1.5	<0.001
15%	1.9	<0.001
20%	1.7	<0.002

Questions?