Causal inference with time-to-event outcomes under competing risk

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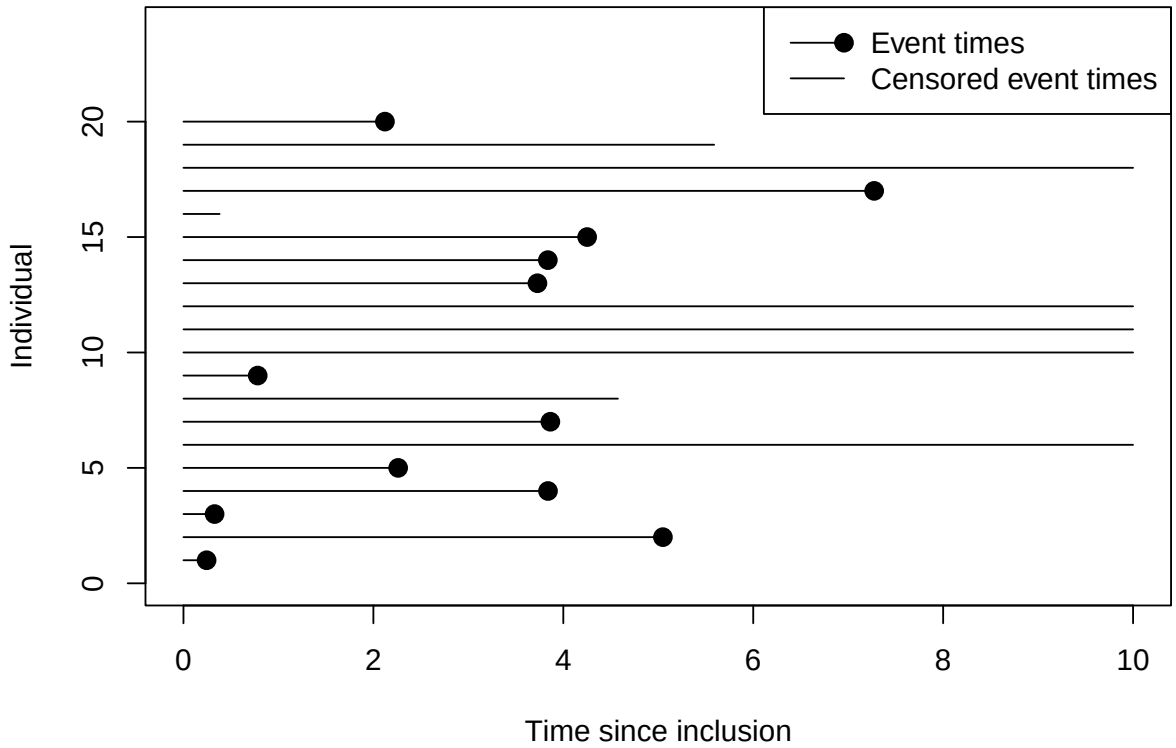
Thanks to Bjarte Aagnes, Tor Åge Myklebust and Paul Lambert for Stata input

Outline

1 The problem of competing risks

- Let us consider possibly right censored event times:



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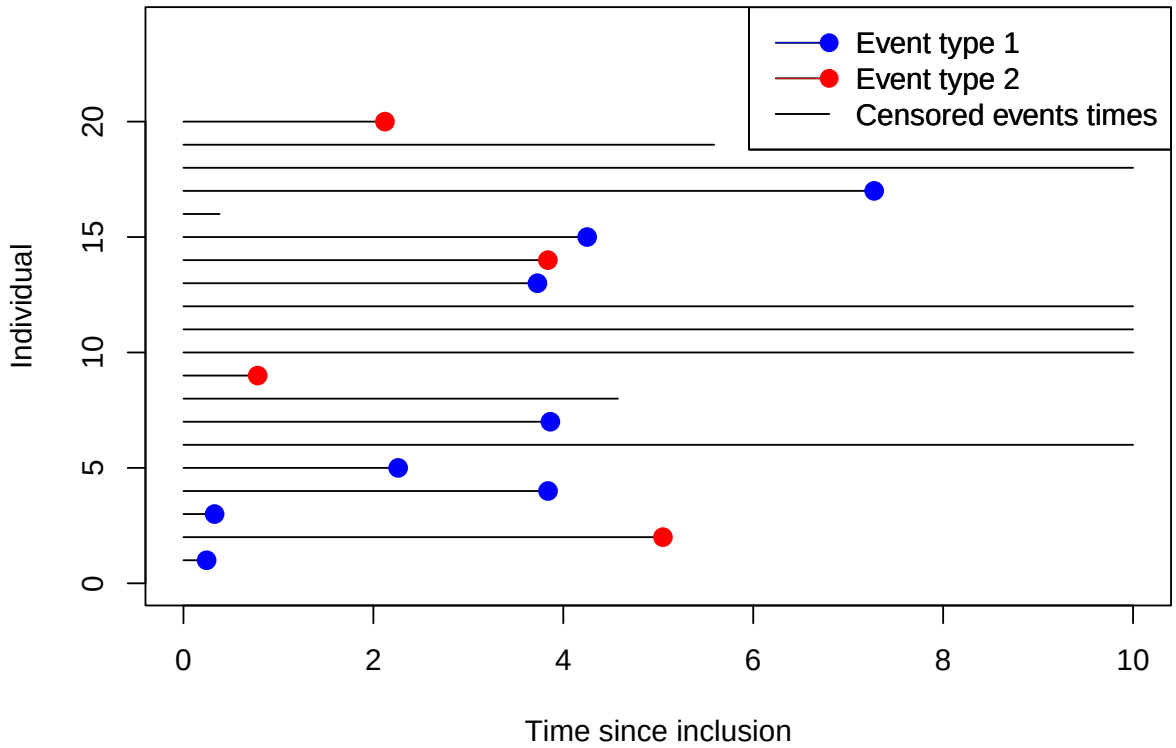

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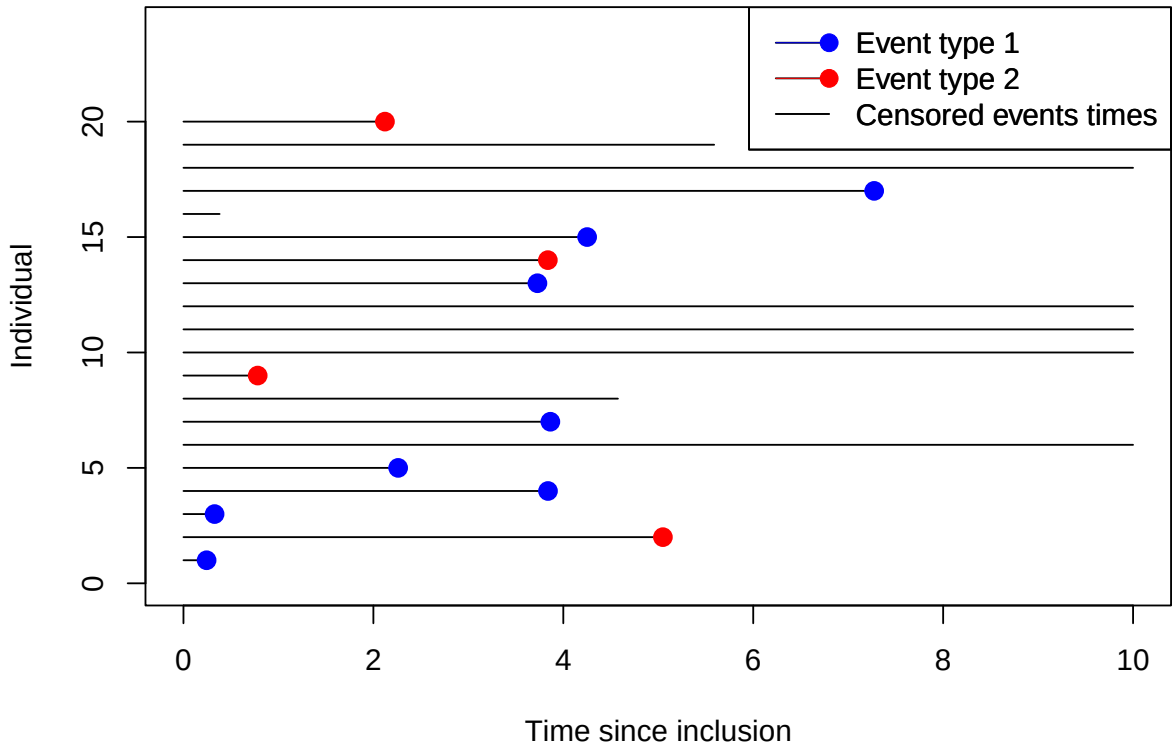

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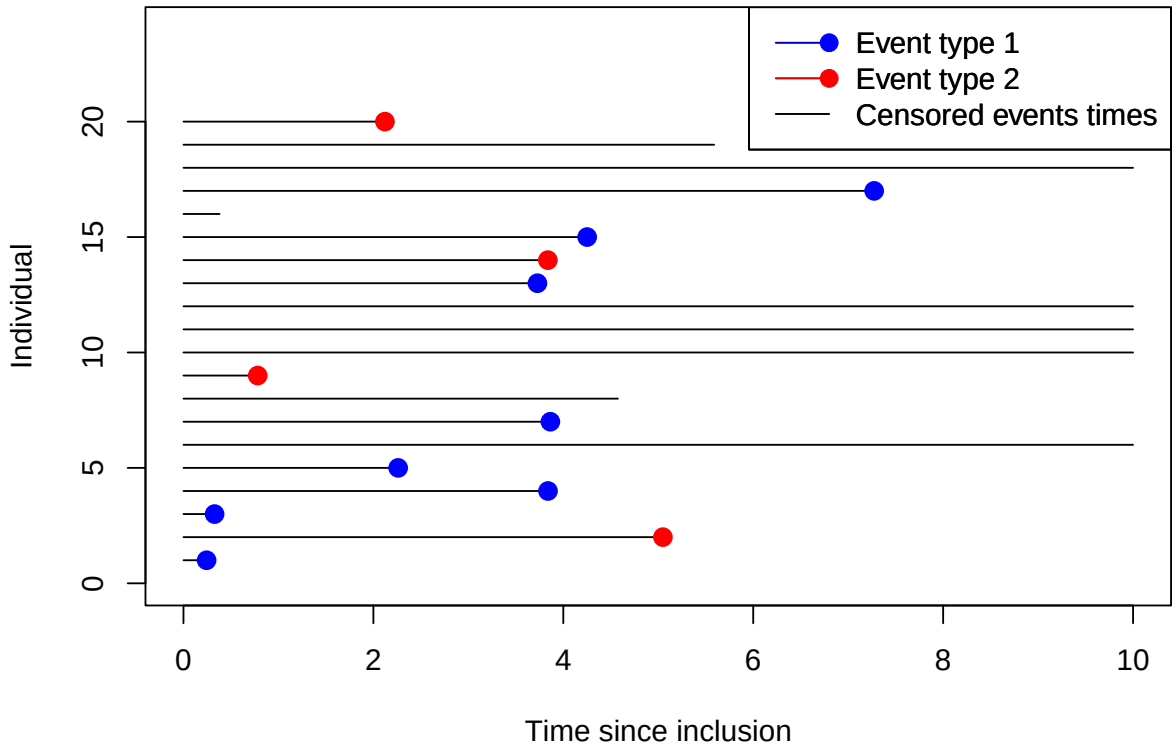

Interest might be in **events of only one type** (e.g. red)

For example; cancer specific death (with the competing event of death from other causes) or the positive event of return-to-work after traumatic injury (with the negative competing event of death)

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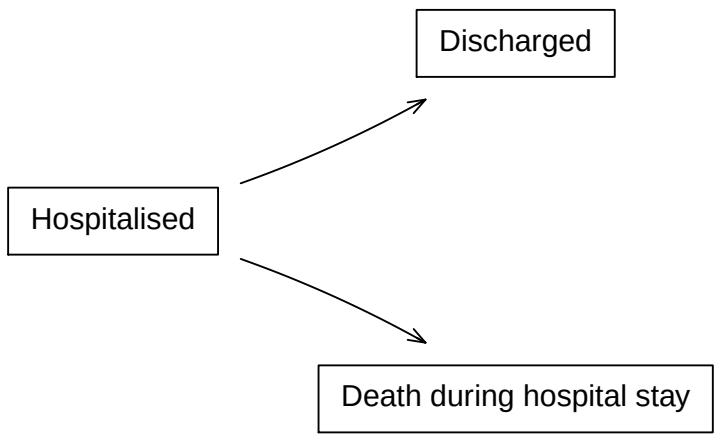

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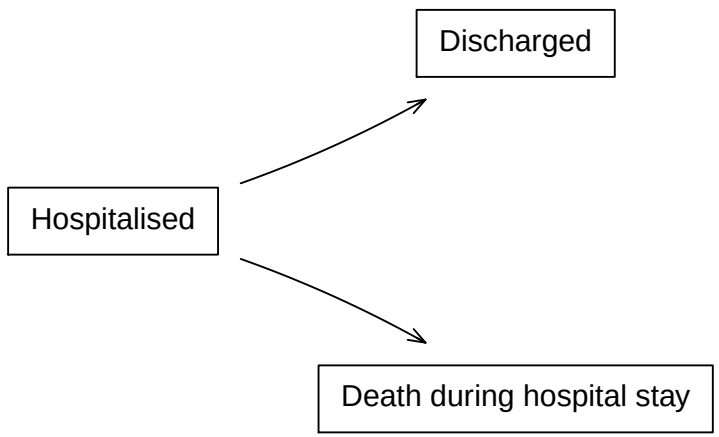

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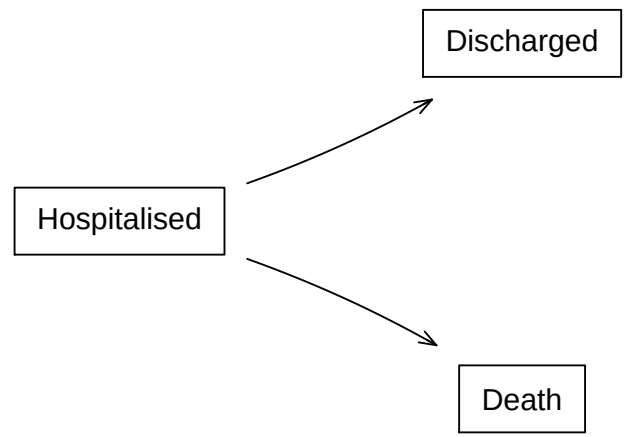

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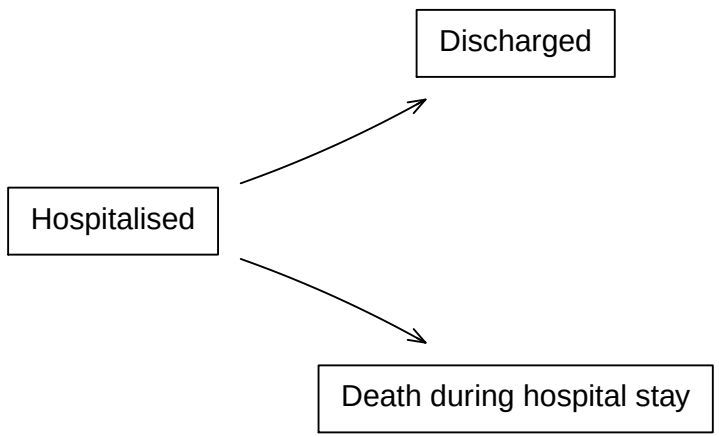

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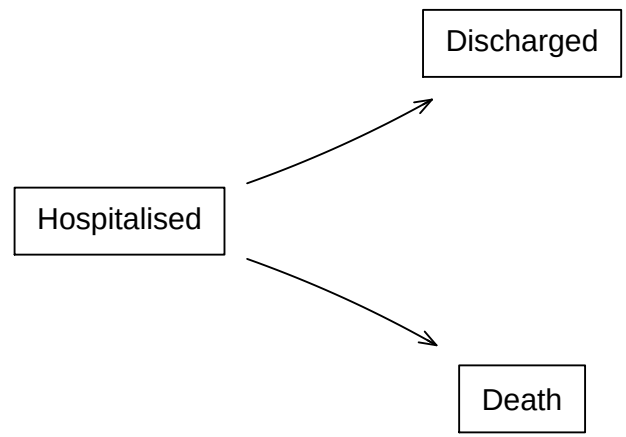

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- Treated by **Bernoulli (1766)**, Florence Nightingale (1860), Neyman (1950), Andersen et al. (2012) and many others

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  When are the independent censoring assumptions reasonable?

2 Classical survival methods for competing risks

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- The cause specific **cumulative incidence function** at time t,

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- The cause specific **cumulative incidence function** at time t,

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for a given cause $j \in \{1, ..., J\}$

- Only meaningful to consider the **overall survival function**,

$$S(t) = \mathbb{P}(T > t) = 1 - \sum_{j=1}^{J} (F_j(t)),$$

which only can be constructed from *all* the cause specific cumulative incidence functions

- Can also consider the **cause specific hazard function** at time t,

$$h_j(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \mathbb{P}(t \leq T < t + \Delta t, Y = j \mid T \geq t),$$

which is the rate of (only) events by cause j, in small time intervals $t + \Delta t$, among those who have not yet died by any cause

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Now have $S(t) = \exp\{-\left(\sum_{j=1}^{J} \int_0^t h_j(s)ds\right)\}$ and $F_j(t) = \int_0^t S(s)h_j(s)ds$

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- The **subdistribution hazard function** has also been suggested;

$$\tilde{h}_j(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \mathbb{P}(t \leq T_j < t + \Delta t, Y = j \mid T_j \geq t),$$

where $T_j = T \times I(Y = j) + \infty \times I(Y \neq j)$

Competing risk data

- Let us now consider the following **data structure**:

```
. list in 1/6

     +---------------------------------+
     | id   A          L          T   D |
     |---------------------------------|
  1. |  1   0   4.579293   12.72125   0 |
  2. |  2   0   3.884528   14.63008   2 |
  3. |  3   1   67.89856   12.08012   1 |
  4. |  4   0   27.68397   20.87179   2 |
  5. |  5   0   5.103034   15.05113   2 |
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Simulated data, where we can imagine that A denote two treatments given at time zero, and L a variable that affects both treatment choice and time to event of interest

The Kaplan-Meier estimator

- Easy to produce a **"cause specific" survival** curve:

```
stset T, fail(D == 2) id(id)
sts graph, by(A) plot1opts(lcolor(black)) plot2opts(lcolor(red)) ytitle("Survival
probability") xtitle("Time") legend(ring(0) pos(1)) title("") ylab(, nogrid) xlab(, nogrid)
plotregion(lstyle(refline))
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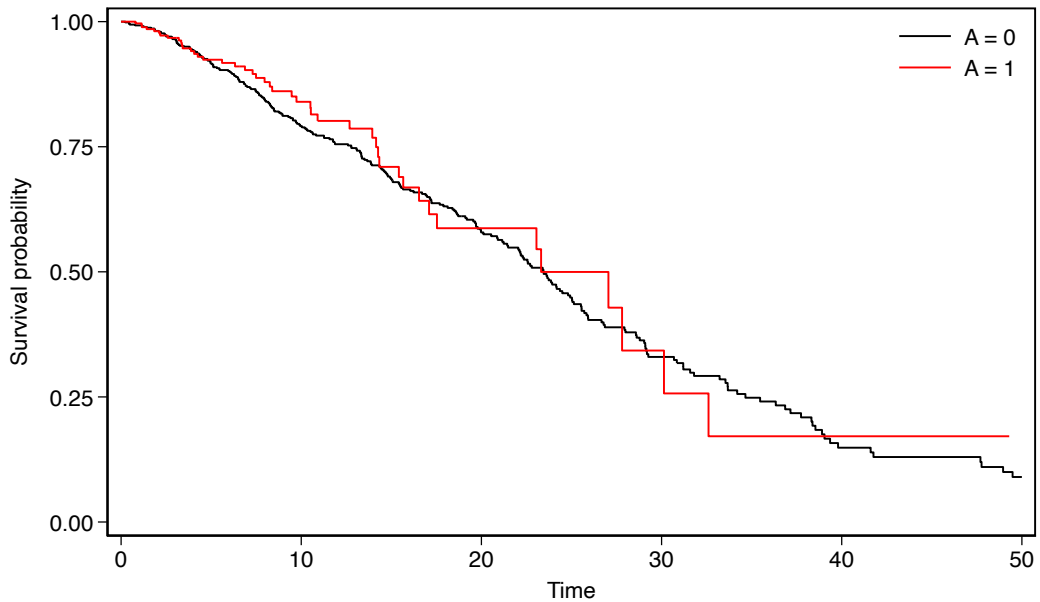

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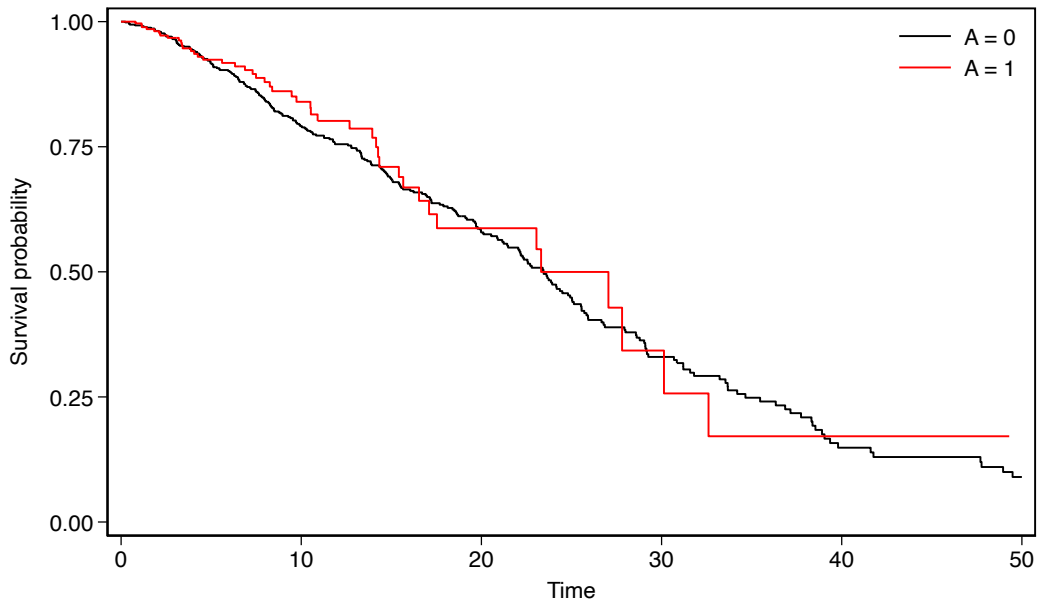

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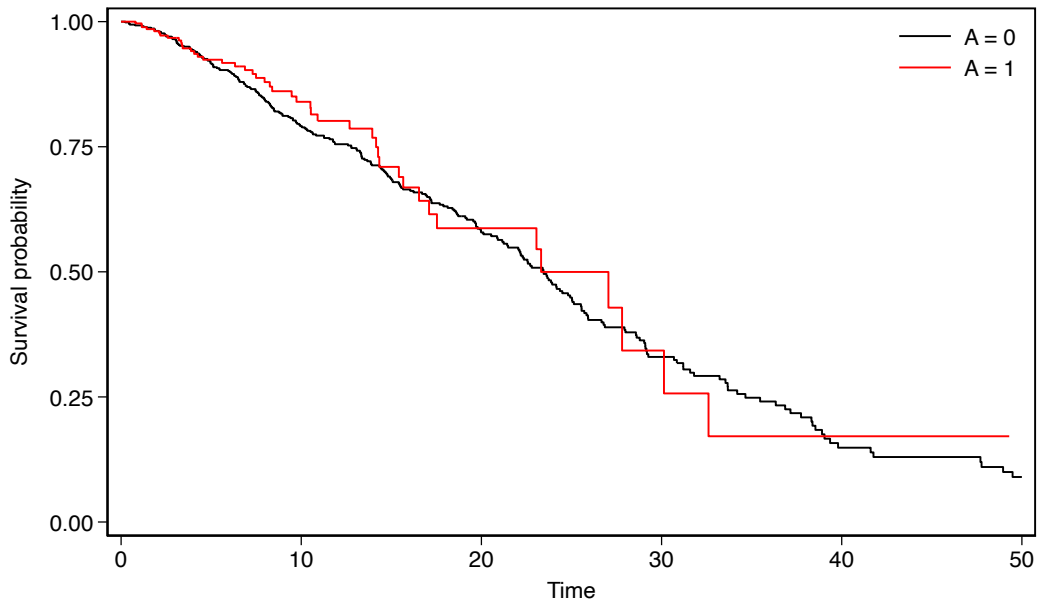

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(data has 429 events (type 2), 500 competing events and 71 censored)

The Nelson-Aalen estimator

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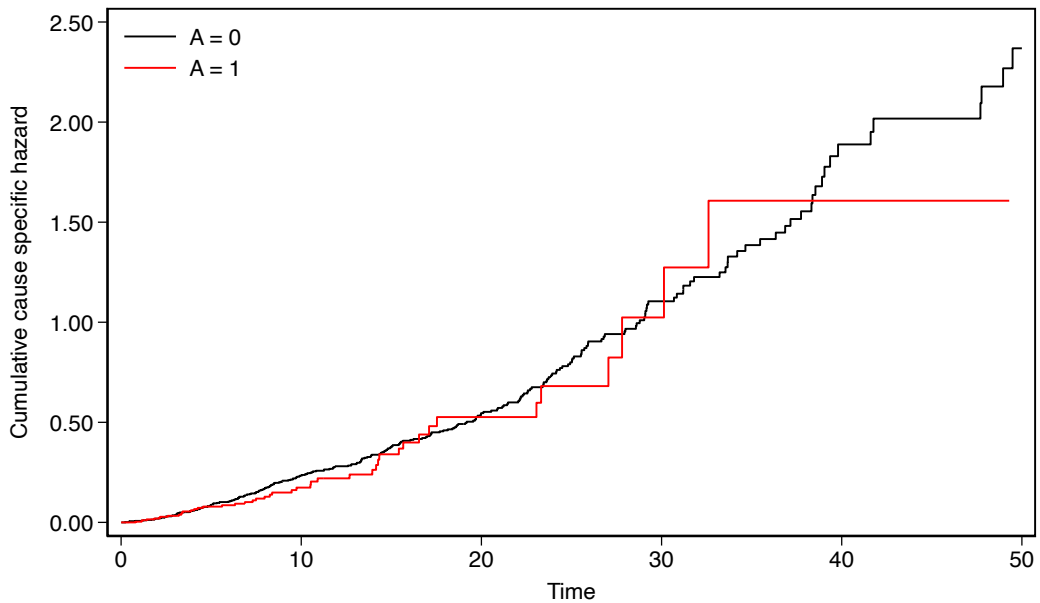

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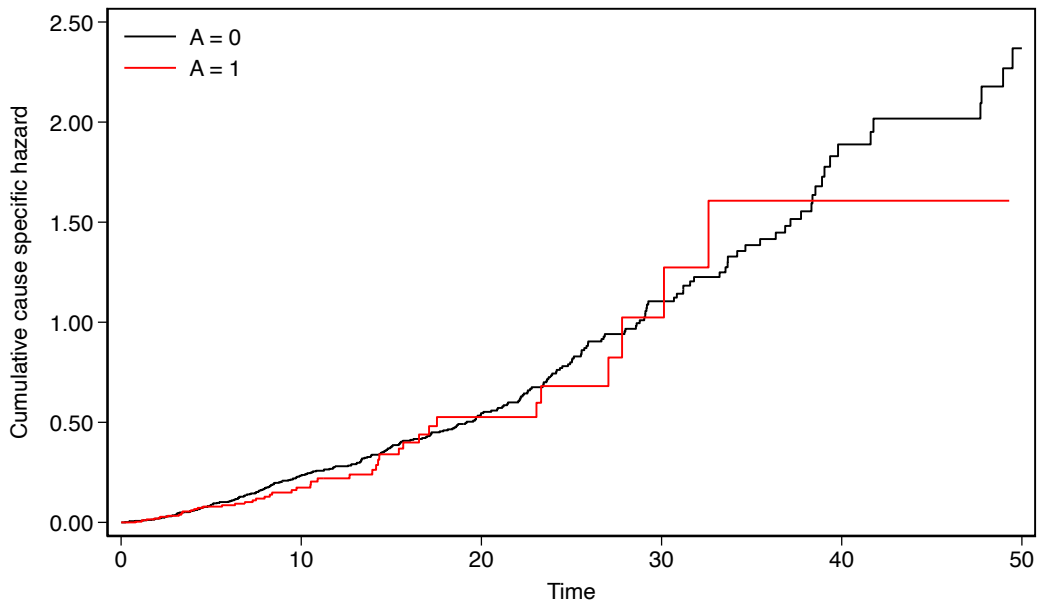

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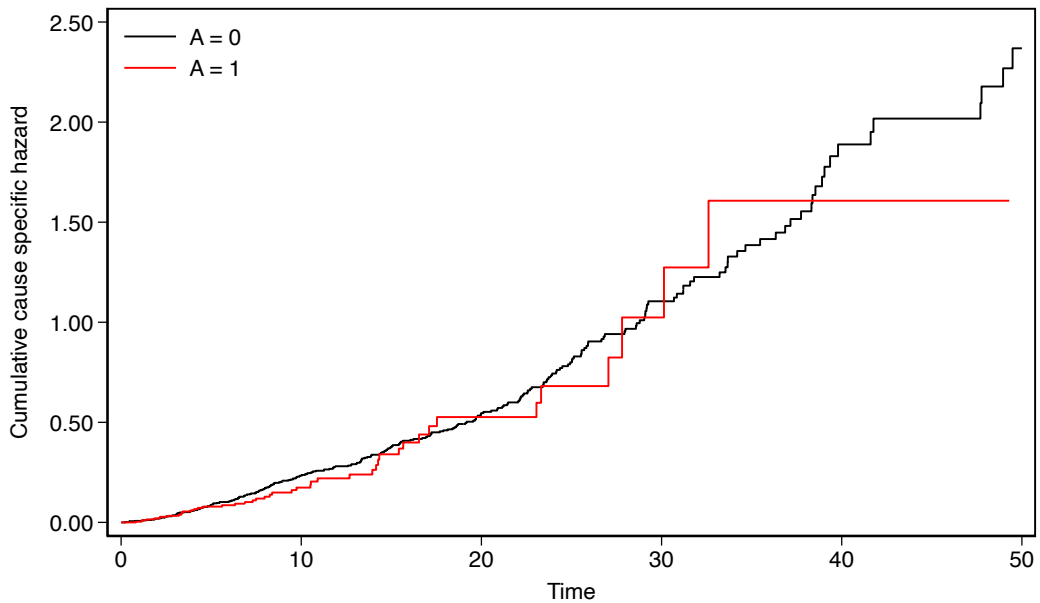

These curves *can* be interpreted as describing the movement from the "alive" state to the "event 2" state

But, the shape of these (cumulative) hazards is now a result of i) individual risk, ii) selection, and iii) rate of competing events

The Aalen-Johansen plug-in estimator

- Can also calculate **cause specific cumulative incidence**, where competing events are allowed:

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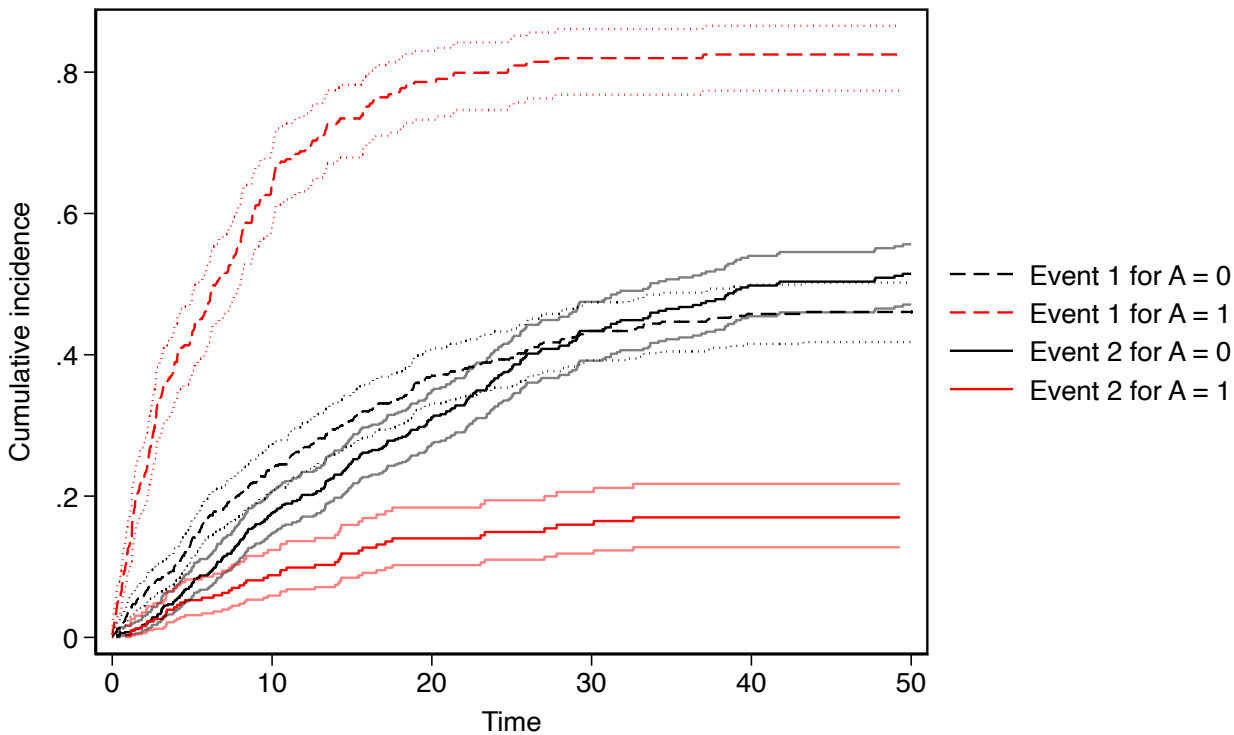

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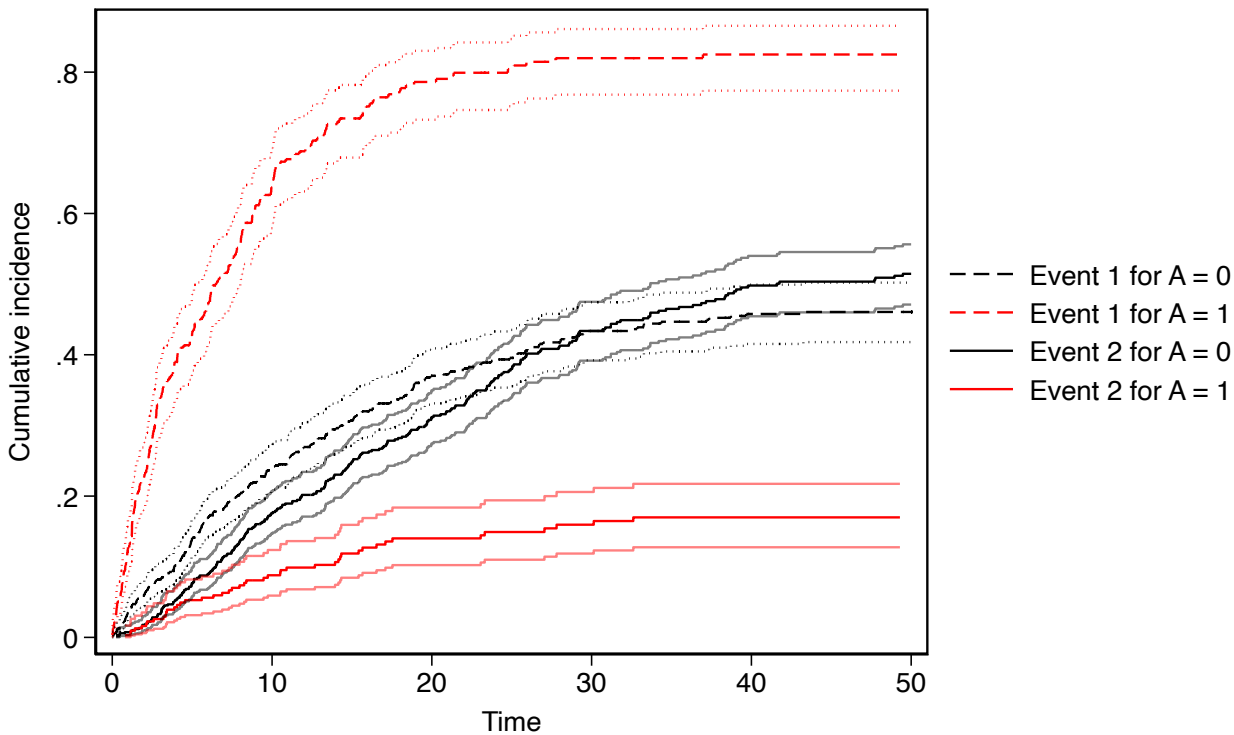

This give a very different picture than cumulative incidence from Kaplan-Meier (1-KM two slides back), which always will overestimate the incidence in the presence of competing events

- Note that, under competing risk, the cumulative incidence is

$$F_j(t) = \int_0^t S(t) h_j(t),$$

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- A general **"empirical transition matrix"** estimator given by Aalen and Johansen (1978):

$$\hat{\mathbf{P}}(0,t) = \pi_0 \prod_{u \in (0,t]} (\mathbf{I} + d\widehat{\mathbf{A}}(u)),$$

where π_0 is the initial state distribution vector (for us $\{1,0,0\}$) and $\widehat{\mathbf{A}}(u))$ is the cumulative transition hazard matrix

Cause specific hazard models

- Common to also fit **Cox models for cause specific hazards**, e.g. using `stcox A`:

```
...
Cox regression with no ties

No. of subjects =      1,000                          Number of obs =  1,000
No. of failures =        315
Time at risk    = 11,185.729
                                                      LR chi2(1)    =   0.49
Log likelihood = -1759.2309                           Prob > chi2   = 0.4848

------------------------------------------------------------------------------
          _t | Haz. ratio   Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
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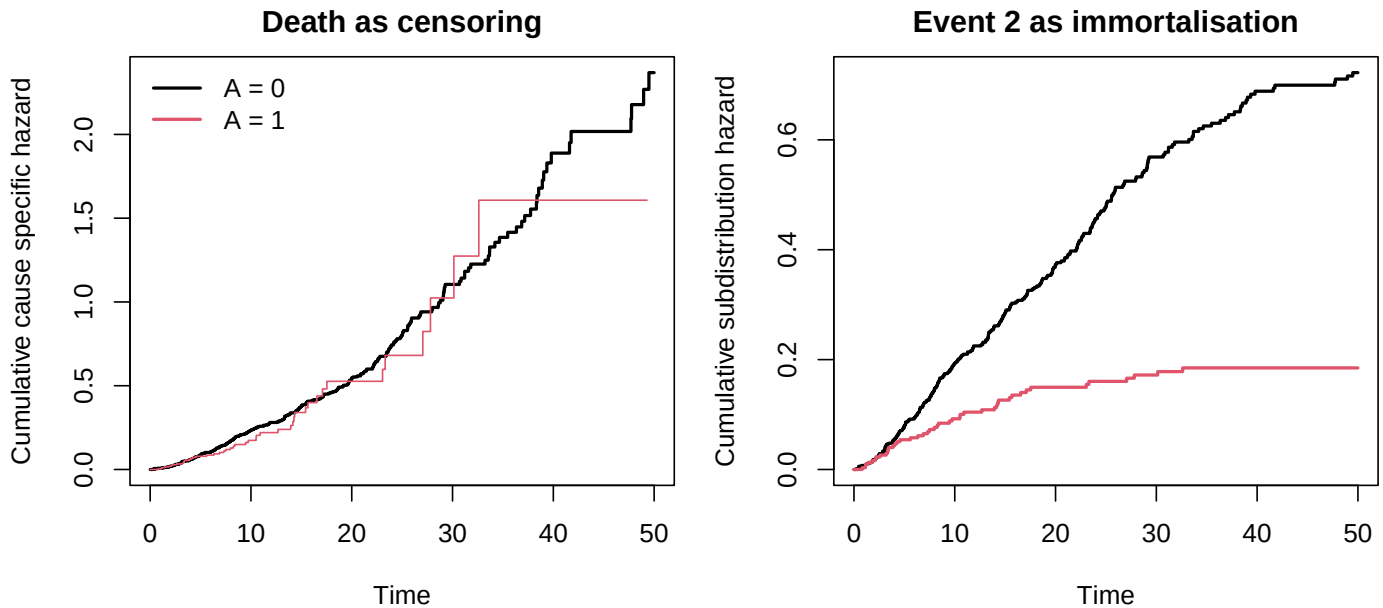
Tempting because it is easy, but this HR can be hard to motivate (useful component for calculating cumulative incidence though)

The Fine and Gray model

- Fine et al. (1999) showed that the one-to-one correspondence can be restored by estimating **the subdistribution hazard**, identified (in a censor free world) by setting all competing event times to ∞



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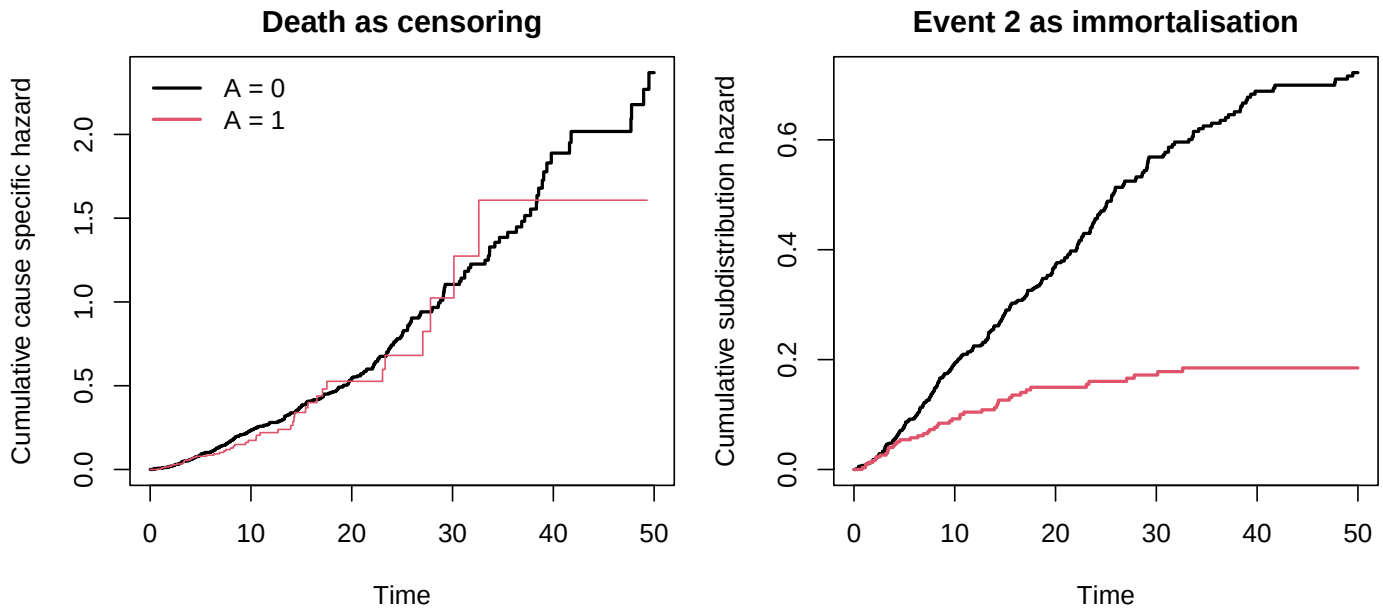

Interpretation is awkward, but this makes 1-KM in the subdistribution data equal to the real world $F_j(t)$

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- See also `stcrreg A compete(D == 2)`, fitting **the Fine and Gray model**, corresponding to a (weighted) Cox model on the subdistribution dataset:

```
...

Competing-risks regression                          No. of obs      =      1,000
                                                    No. of subjects =      1,000
Failure event:   D == 2                             No. failed      =        315
Competing event: D == 1                             No. competing   =        500
                                                    No. censored    =        185


                                                    Wald chi2(1)    =      51.90
Log pseudolikelihood = -1999.7238                   Prob > chi2     =     0.0000

                                (Std. err. adjusted for 1,000 clusters in id)
------------------------------------------------------------------------------
             |               Robust
          _t |        SHR   std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
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- See also `stcrreg A compete(D == 2)`, fitting **the Fine and Gray model**, corresponding to a (weighted) Cox model on the subdistribution dataset:

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Competing-risks regression                          No. of obs      =      1,000
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Failure event:   D == 2                             No. failed      =        315
Competing event: D == 1                             No. competing   =        500
                                                    No. censored    =        185


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Log pseudolikelihood = -1999.7238                   Prob > chi2     =     0.0000

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[1] For regression of $F_j(t)$, see also pseudo values (Klein et al. 2005)

An example (out of many)

thebmj covid-19 Research Education News & Views Campaigns Jobs

Research

Covid-19 vaccine effectiveness against post-covid-19 condition among 589 722 individuals in Sweden: population based cohort study

BMJ 2023 ; 383 doi: https://doi.org/10.1136/bmj-2023-076990 (Published 22 November 2023)
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Linked Editorial
Does timely vaccination help prevent post-viral conditions?

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  Compare vaccinated and unvaccinated (from time of infection)

  After covid infection people can get PCC, but are censored if they get vaccinated, reinfected, emigrate or die

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	Not vaccinated before covid-19 n = 290,030	Vaccinated before covid-19 n = 299,692
Vaccination, n (%)	200,965 (69)	167,000 (56)
Reached end of follow-up[1], n (%)	73,872 (26)	126,835 (42)
Reinfection[2], n (%)	9,613 (3.3)	3,275 (1.1)
PCC, n (%)	4,118 (1.4)	1,201 (0.4)
Death, n (%)	821 (0.3)	1,076 (0.4)
Emigration, n (%)	641 (0.2)	305 (0.1)

[1]30 November 2022.
[2]New covid-19 infection at least 90 days after covid-19 index date.

PCC=post-covid-19 condition

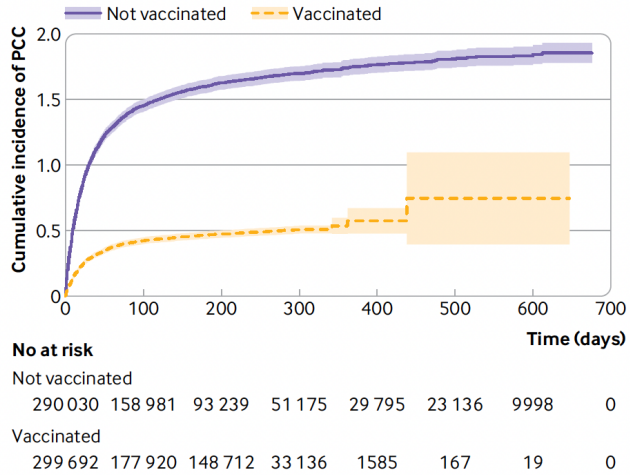

Fig 2 | Cumulative incidence of PCC, using Kaplan-Meier failure function, for individuals vaccinated or not vaccinated against covid-19. Study population included all adult (≥18 years) residents in the two largest regions of Sweden with covid-19 first registered during the study inclusion period, 27 December 2020 to 9 February 2022. PCC=post-covid-19 condition

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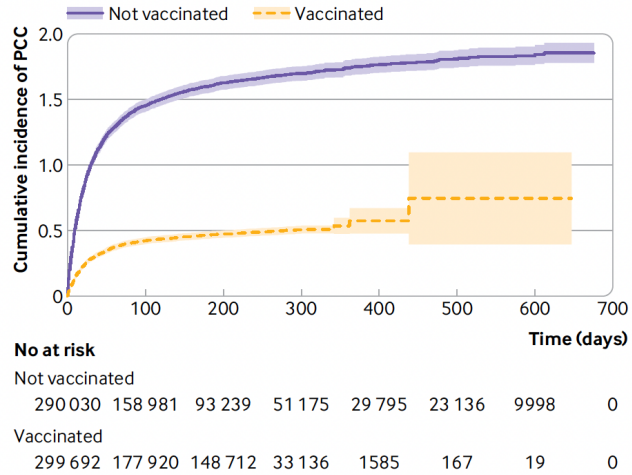

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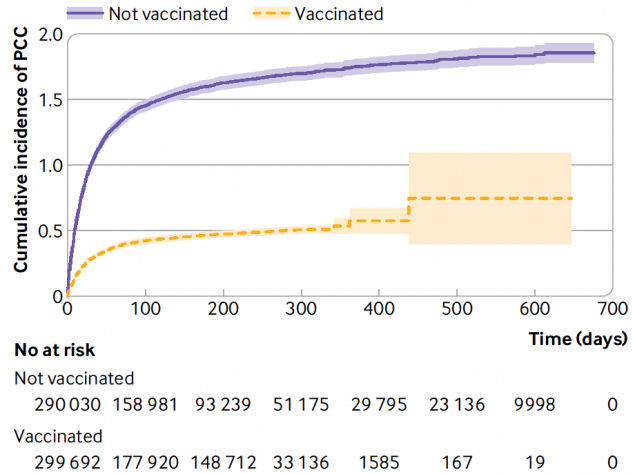

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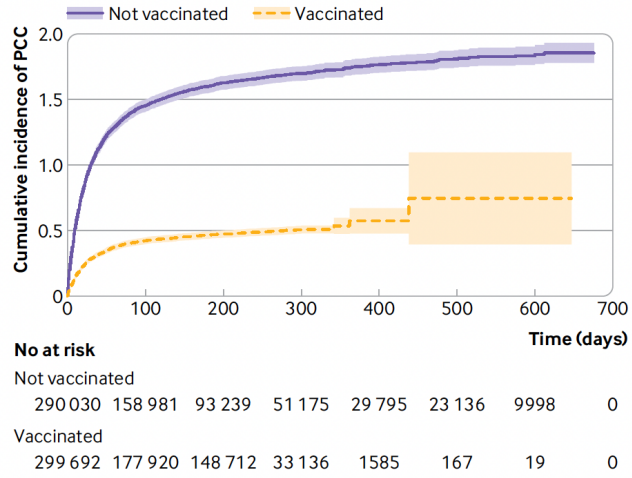

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(paper generated a lot of discussion, a BMJ editorial, 8 online comments and a correction, but nothing on competing risks)

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Recent developments in the analysis of competing risks

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  Give strategies on how to handle "intercurrent events": *events occurring after treatment initiation affecting interpretation or existence of the measurements associated with the clinical question of interest*

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  ... no reason to start by asking whether to censor or not

Average causal effects

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$$\text{ATE} = \mathbb{E}(Y^1) \text{ vs. } \mathbb{E}(Y^0),$$

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  (contrasts of restricted mean time lost is a related alternative)

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- `stcrreg A, compete(D==1)` give **a weighted test** for difference in cause specific cumulative incidence

- For **time-varying treatment regimes**, more general inverse probability of treatment weighting (IPTW) can be used for

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- **Standardisation/g-formula/robust methods** are alternatives

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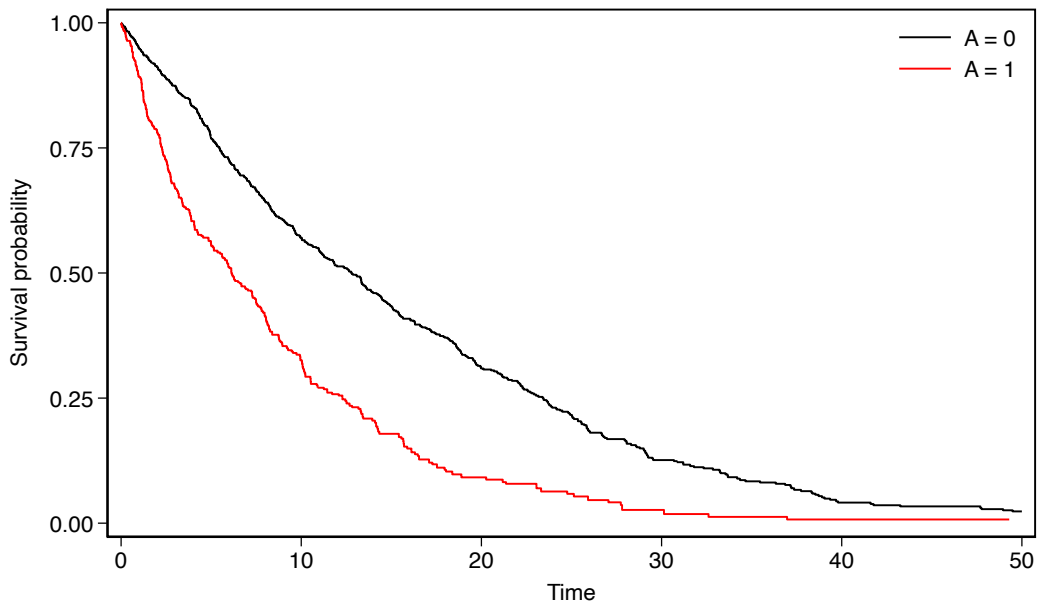

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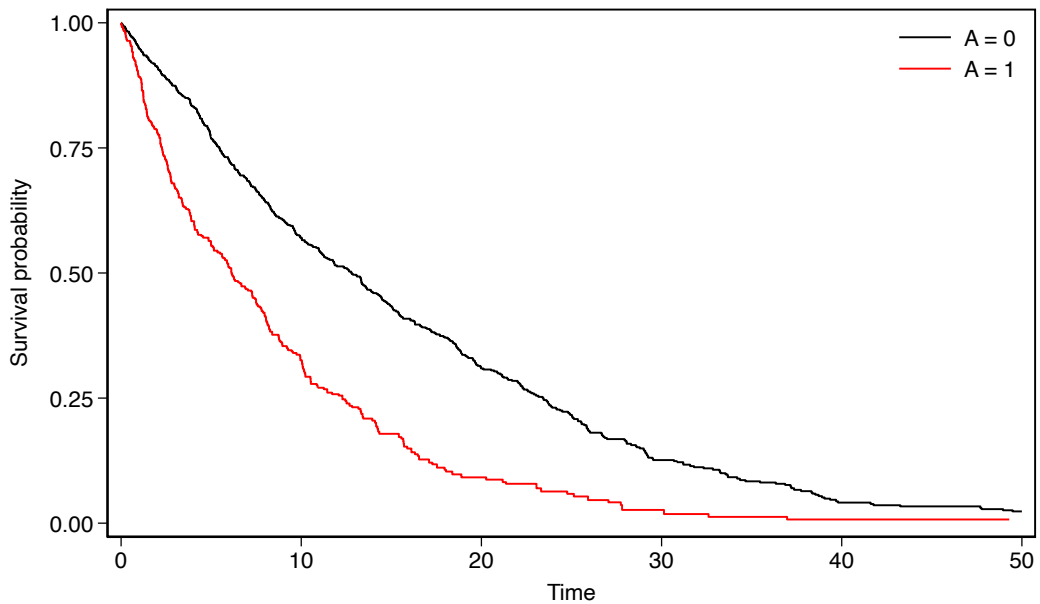

Look at, for example, "death by any cause" or "cancer free survival" and analyse as in simple survival settings

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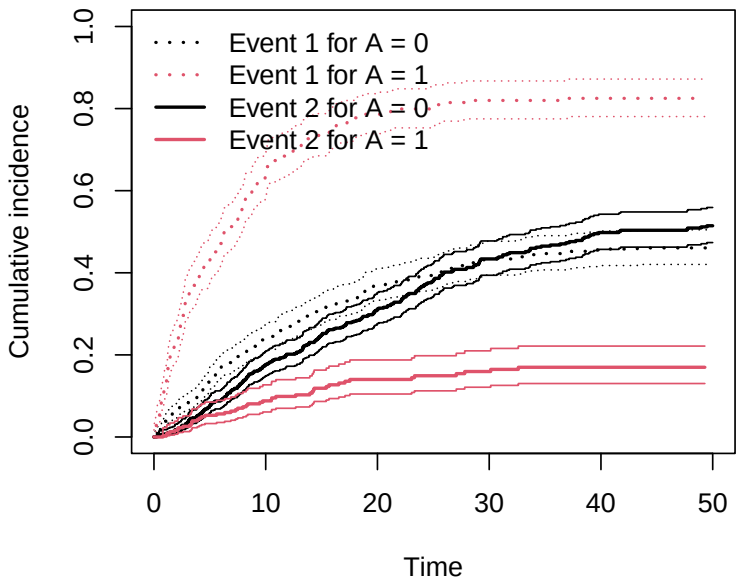

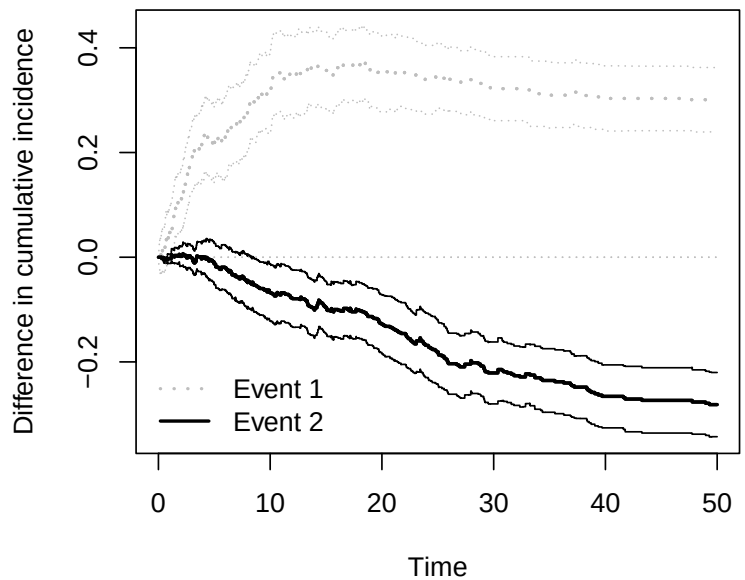

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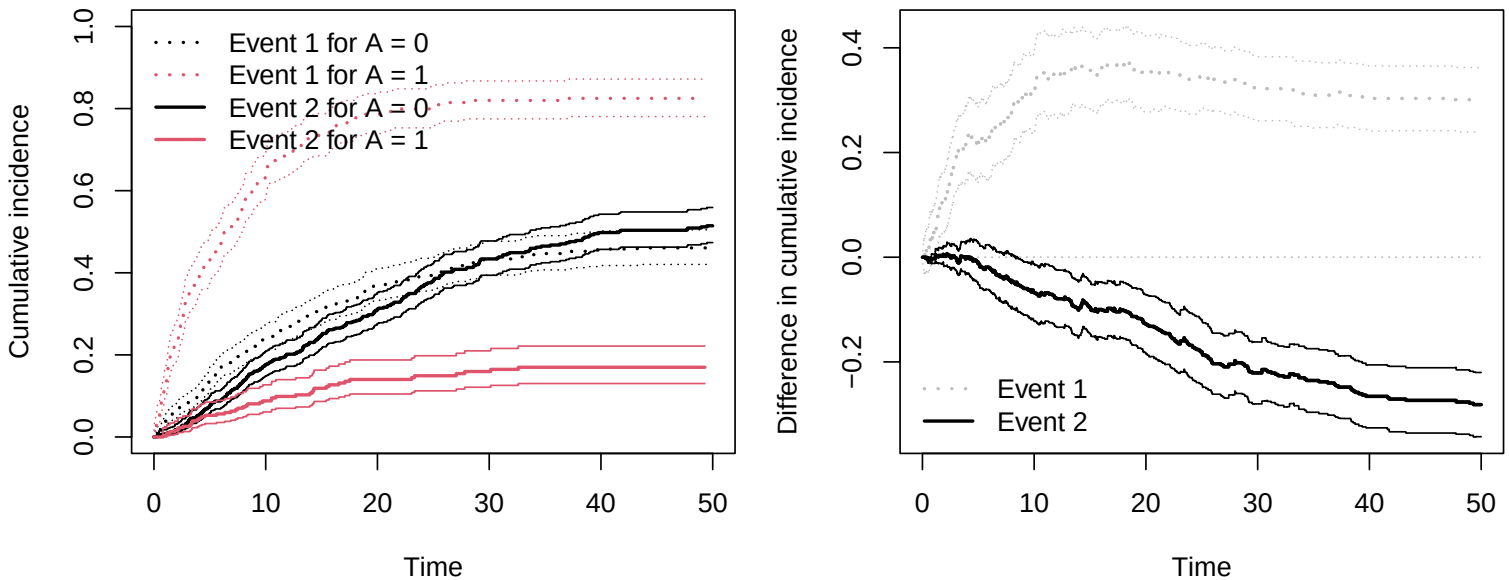

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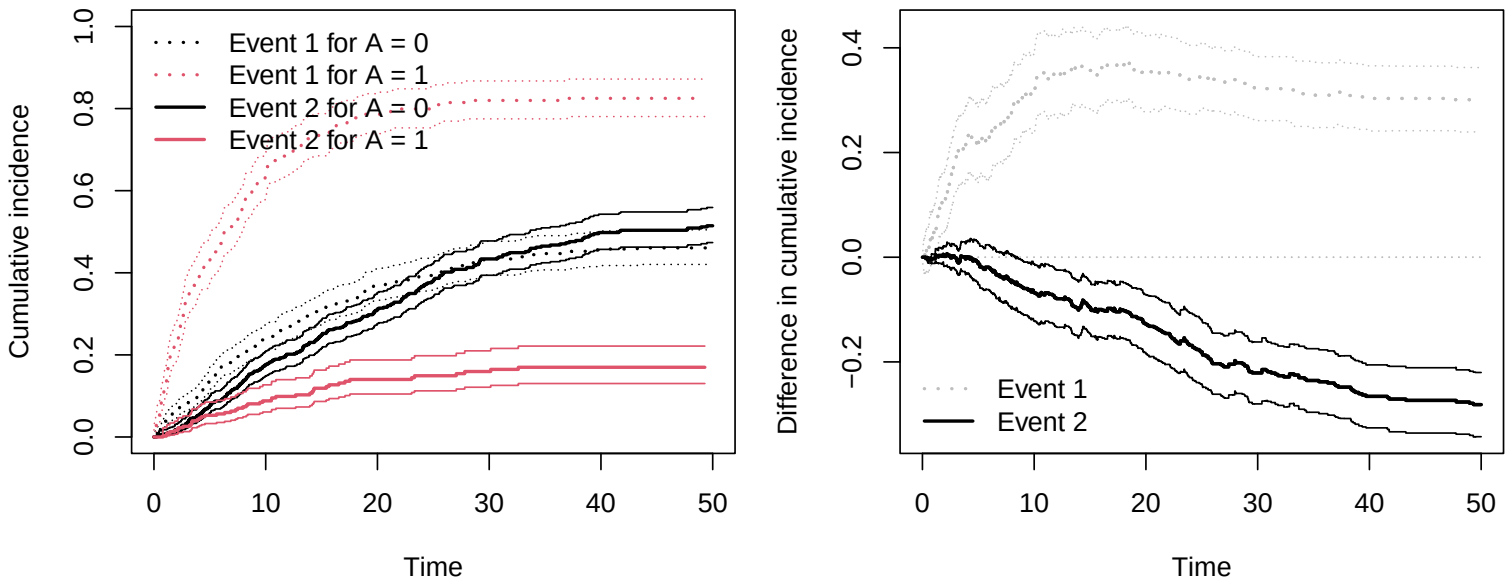

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`stcompet` is unfortunately not reacting well to weights, see `stcrprep` and related functions by Lambert

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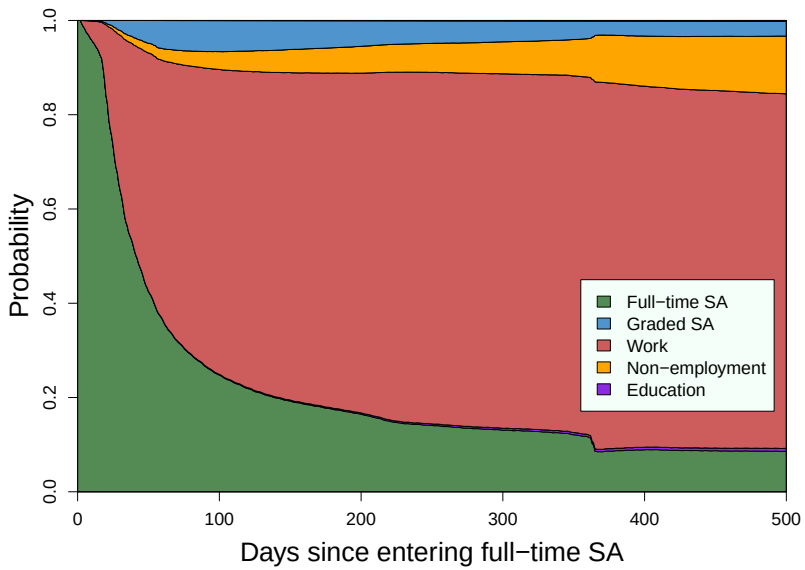

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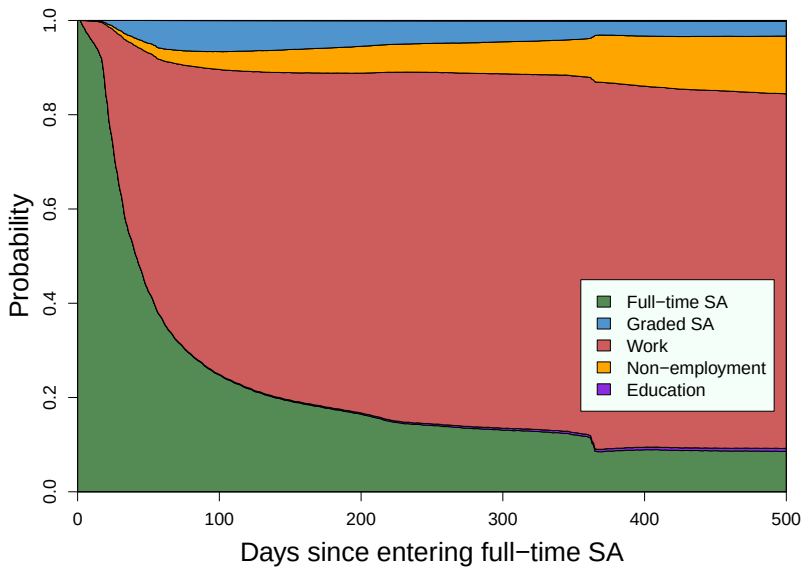

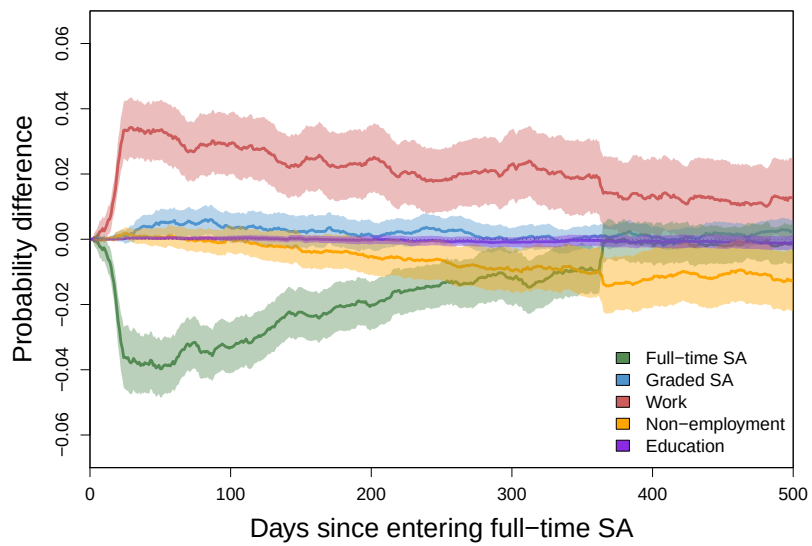

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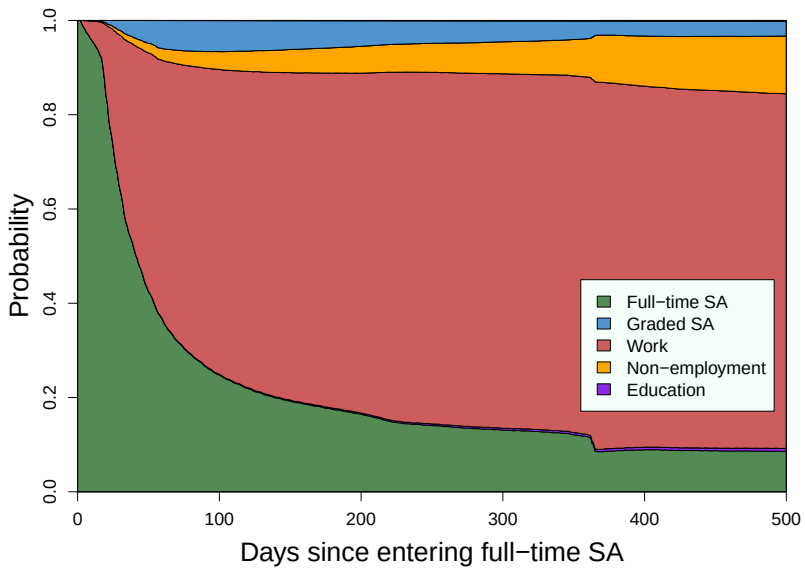

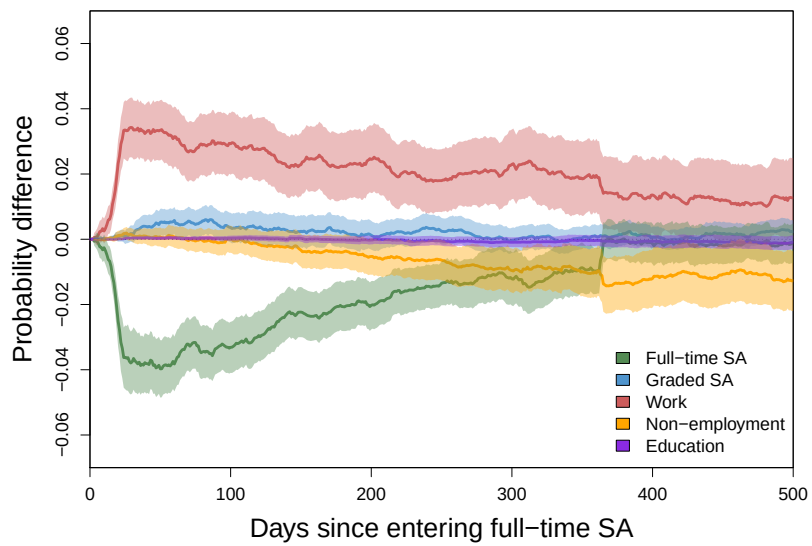

See `multistate` package by Crowther, Lambert and others for (mostly flexible parametric?) options in Stata

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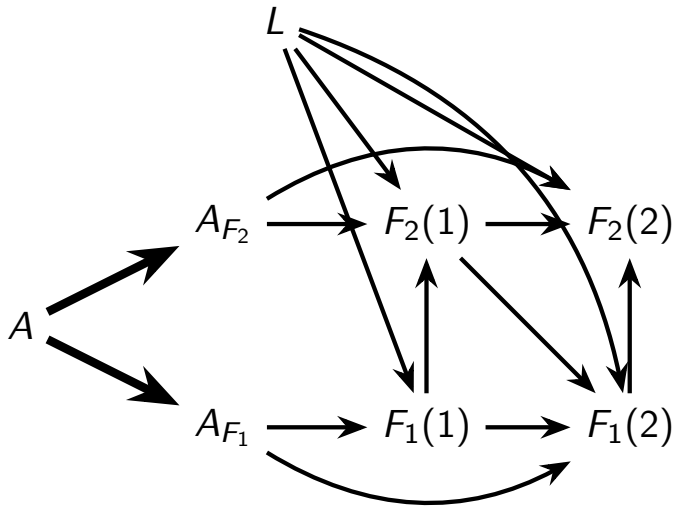

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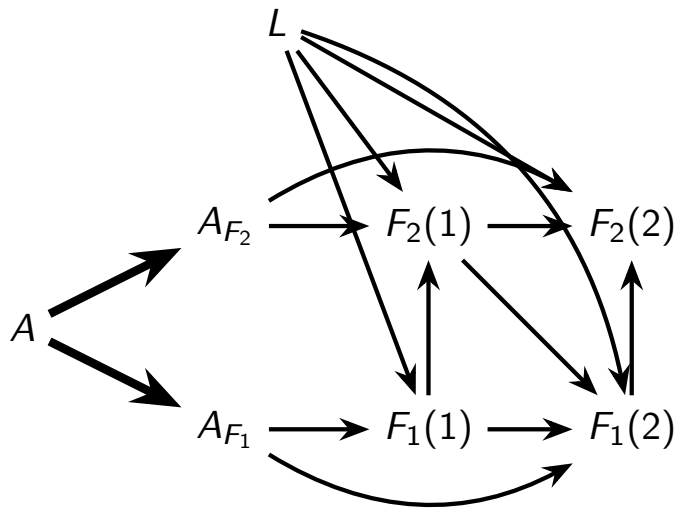

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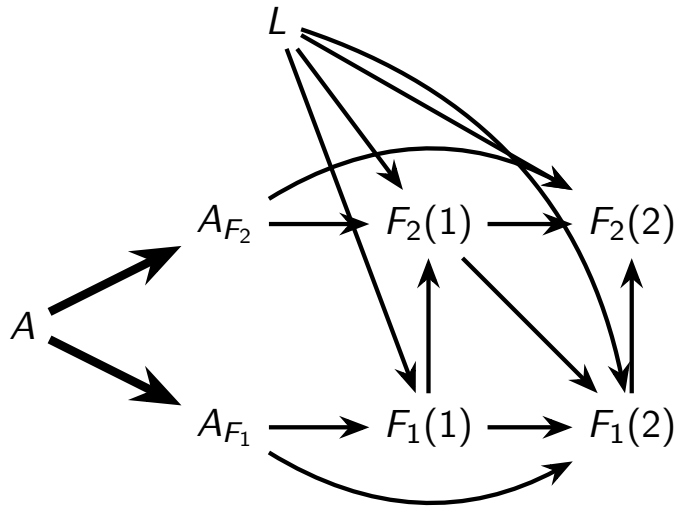

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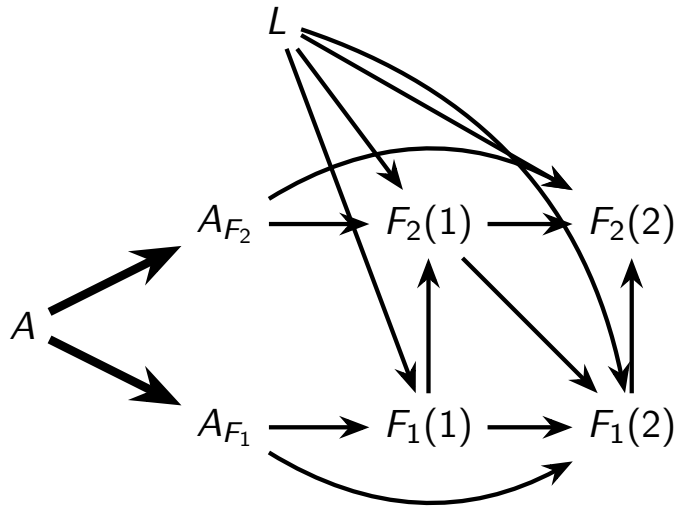

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  See also sequential trials (Gran et al. 2010, Keogh et al. 2023)

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  51 had competing events and **only 26 (51%) dealt with it adequately**

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