Survival Analysis IV

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Competing Risks

Survival Analysis

- Observed survival data:

  Y = time to failure event or lost to follow-up, whichever occurred first

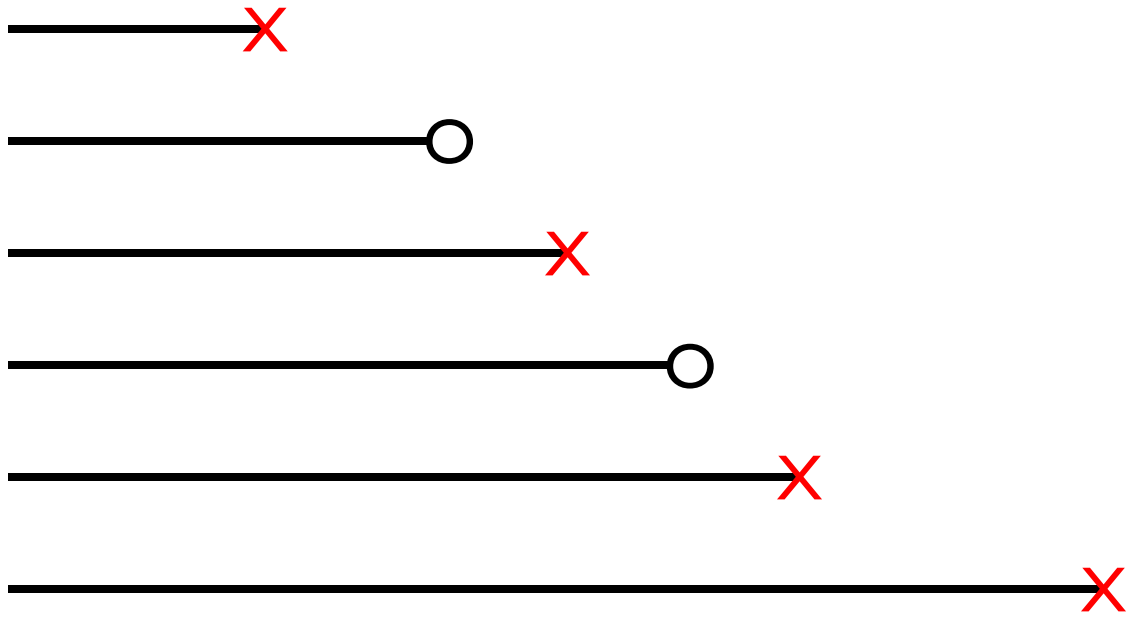
  Δ = 1 if failure event was observed
  = 0 if censoring was observed

- Goal: make inference about time to failure event had all subjects were followed until failure

Complication arises due to censoring

- The event time is unknown for patients who lost to follow up
- **Elimination:** extrapolate to a scenario in which censoring never happens
- This can be achieved by assuming that censoring is independent of survival time (analogous to "missing completely at random" in one sample setting and "missing at random" in regression setting)
- Kaplan-Meier curves estimates the survival probability in the perfect scenario where all subjects were followed until they experience the failure event

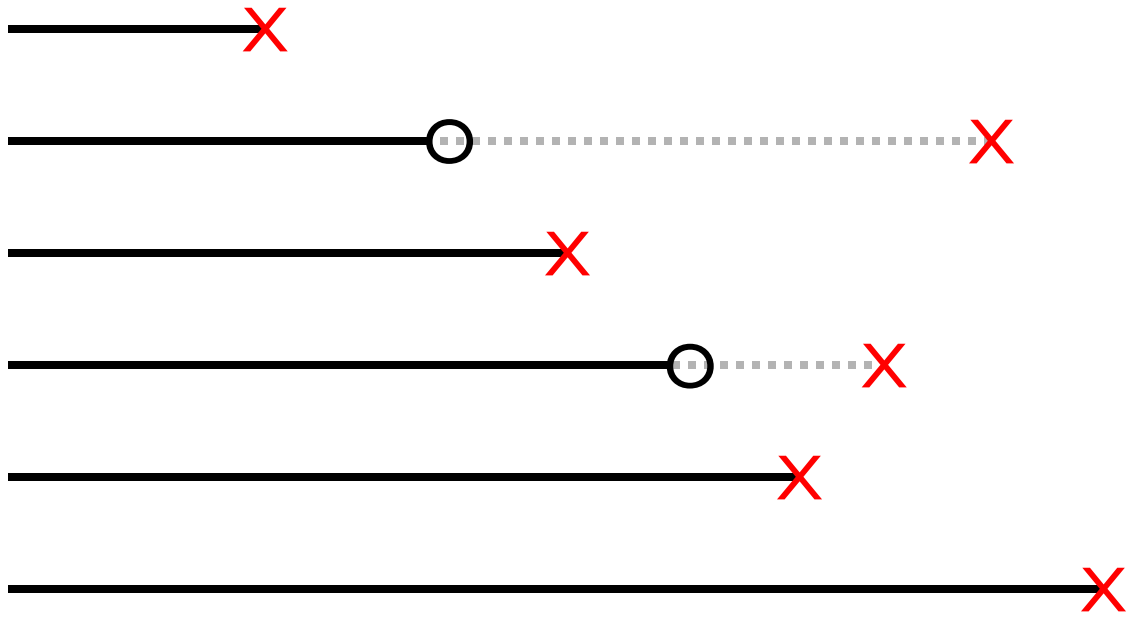
Extrapolate to eliminate incomplete follow up



X: event time

O: lost to follow up

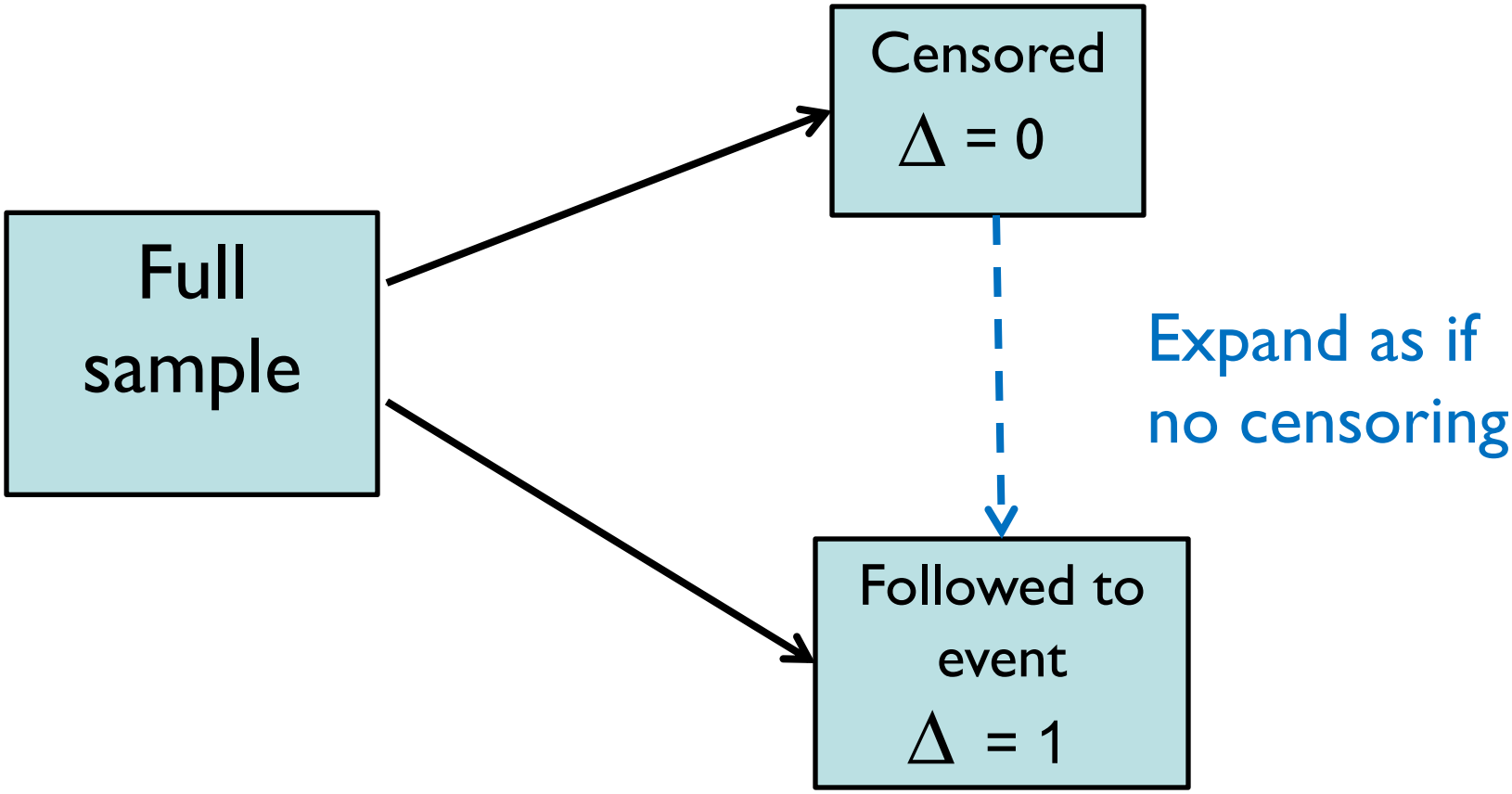
Extrapolate to eliminate incomplete follow up



X: event time

O: lost to follow up

Elimination



Competing Risks

- Competing risks analysis mostly concerned with when non-related death can occur – potentially excluding the event of interest
- Remember conventional Kaplan-Meier – subject lost to follow up → number of subjects "at risk" drops by one
  - Assumption: independent censoring
  - Objective: extrapolate to "eliminate" incomplete follow up
- But what about death due to "other causes"?
- Assumption and Objective both flawed
  Kaplan-Meier curves are not appropriate for competing risks

Competing Risks

Definition: *Competing risks data* arise when multiple events can occur and follow-up can end due to occurrence of one or more of those types of events, precluding observation of at least one of the other event types

Observed data:

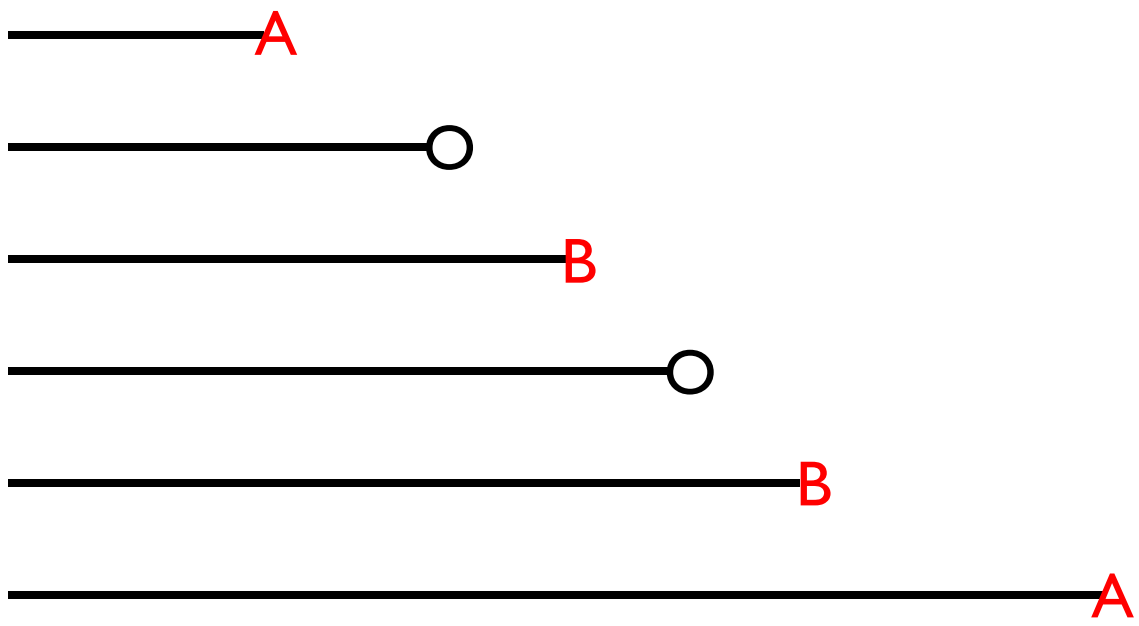
Y: time of first event of any type

Δ = k if the k-th event type occurs first

Censoring in Competing Risks

- Both event time and event type are unknown for patients who lost to follow-up
- **Elimination:** extrapolate to a scenario in which censoring never happens
- This can be achieved by assuming that censoring is independent of event time and event type

Competing risks data

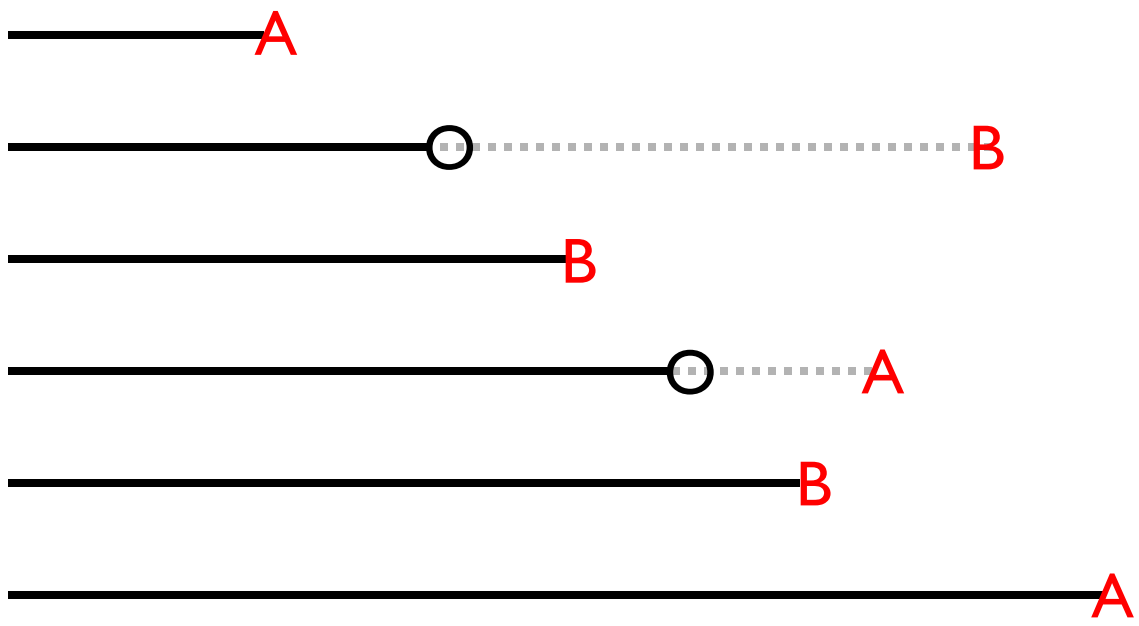


A: fracture;

B: death without fracture;

O: lost to follow up

Extrapolate to eliminate incomplete follow up



A: fracture;

B: death without fracture;

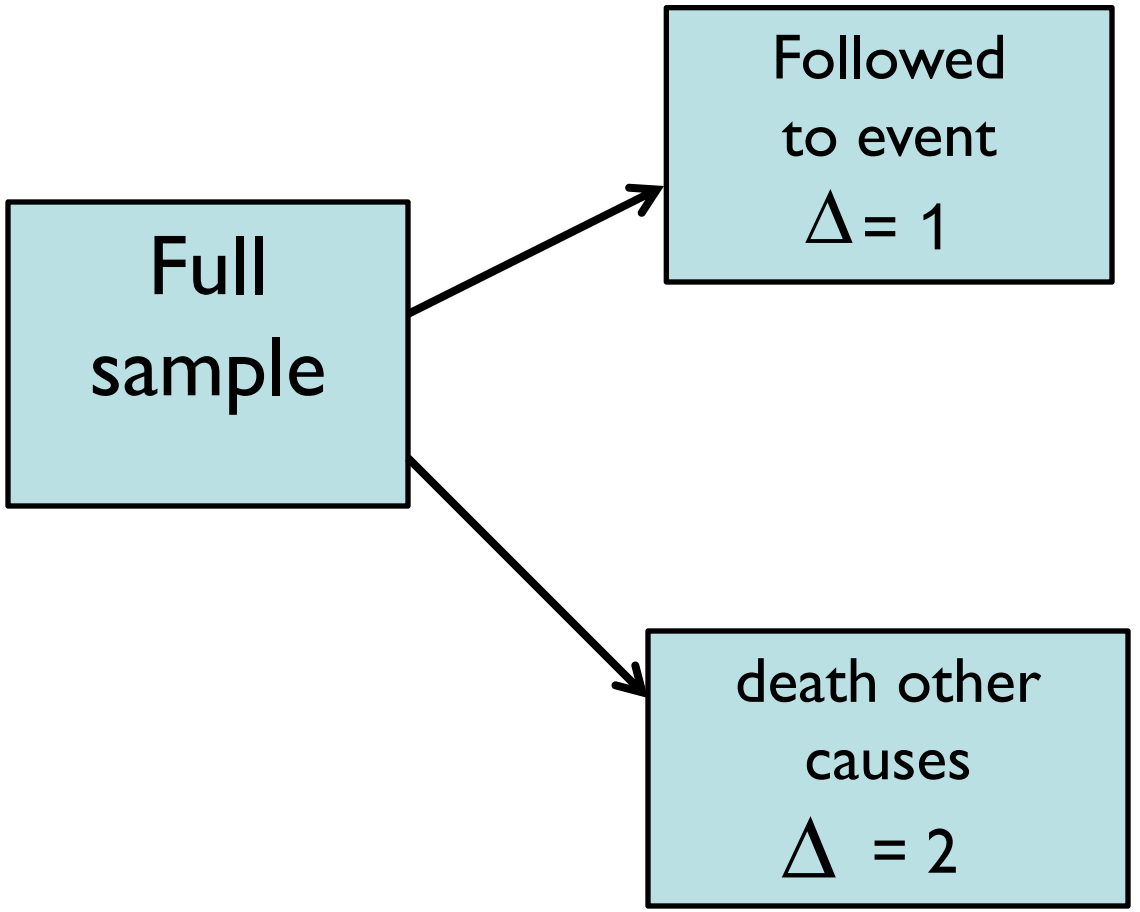
O: lost to follow up

Competing Risks

- **Elimination:** extrapolate to a scenario in which a type of event never happens [e.g.., “loss to follow up” or “incomplete follow up”]

- **Accommodation:** acknowledge and allow for the competing risks – treat the competing risk as excluding the patient from having the event of interest [e.g., death]

Accommodation



Deaths no longer at risk for event of interest

MrOS study

- Study predictors of bone fracture and low bone mineral density (BMD)
- 5993 men over 65 with average 5 year follow-up
- 531 participants fracture, 657 deaths prior to fracture, 4805 alive without fracture

MrOS study

- How well does baseline BMD predict fracture?
- Two sources of incomplete follow-up:

  1) end of observation (loss to follow-up / short observation times due to staggered entry)

  2) death

MrOS data

```
clear
use mros.dta
. list years status bmd3 weight in 1/7
```

	years	status	bmd3	weight
1.	6.518823	0	3	87.8
2.	6.499658	0	2	99.4
3.	6.49692	0	2	83.1
4.	6.49692	0	3	97.4
5.	3.036277	2	3	82.9
6.	6.494182	0	3	76.3
7.	4.50924	1	1	62.8

status
= 0 if censored
= 1 if fracture
= 2 if deaths prior to fracture

Cause-Specific Hazard Function

Definition: The *cause-specific hazard function* for event type, k, $h_k(t)$, is the short-term rate at which subjects experience the onset of the k-th event among those who have not yet experienced the event of interest (e.g., fracture) or a competing event (e.g., death) prior to t.

$$\frac{\text{\# observed k-th events at time t}}{\text{\# at risk of k-th event at time t}}$$

Note: the denominator exclude those who had experienced other competing events prior to t

Cause-Specific Hazard Function

$$\frac{\text{\# observed k-th events at time t}}{\text{\# at risk of k-th event at time t}}$$

- # at risk of k-the event at time t = # alive without fracture immediately prior to time t
- To estimate cause-specific hazard simply set up data as ordinary survival with k-th failure as the only type – all other competing causes (including death) are treated as censored

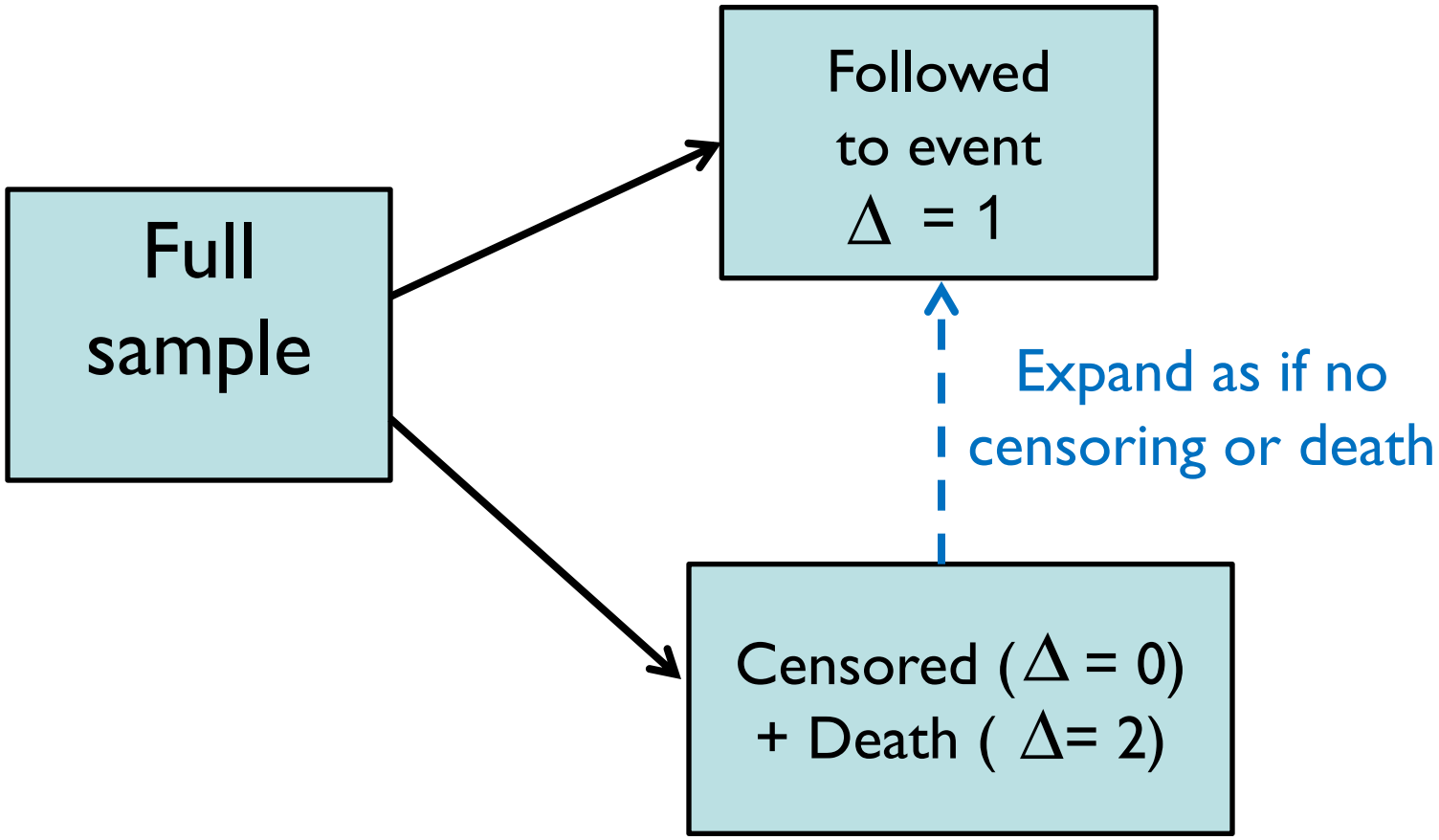
Cause-Specific Hazard Function

Counterintuitive

– cause-specific hazard function does not make a distinction between censoring and death…

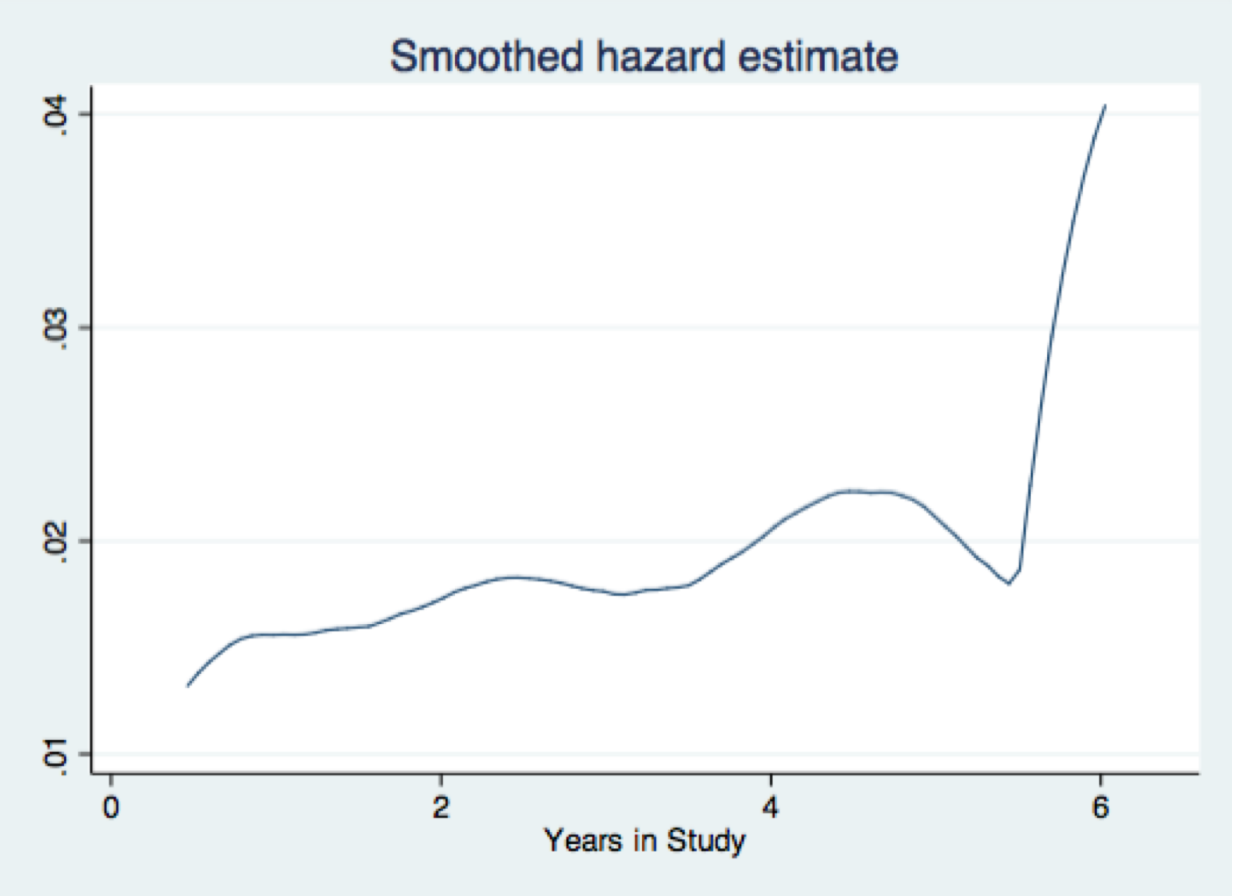
In contrast with *cumulative incidence function*…

Elimination



MrOS cause-specific hazard

```
use mros.dta
stset years, failure(status==1) // fracture is the event
sts graph if _t < 6.5, hazard xtitle(Years in Study)
```



Cox model for cause-specific hazard function

- Model cause-specific hazard function using Cox proportional hazard formulation
- Let $h_k(t)$ be the k-th cause-specific hazard, then…
- $h_k(t|x) = h_{0k}(t) \exp(\beta_{1k}x_1+\ldots+\beta_{pk}x_p)$
- Works same as original Cox model except HRs apply to the k-th cause specific hazard

MrOS Cox model for cause-specific hazard function (for fracture)

```
clear
use mros.dta
gen weight10kg = weight/10
stset years, failure(status==1)
stcox i.bmd3 weight10kg, nolog  // bmd is defined in 3 quantiles

No. of subjects =         5993                 Number of obs   =      5993
No. of failures =          531
Time at risk    =  30483.46339
                                               LR chi2(3)      =    121.22
Log likelihood  =   -4442.2904                 Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        bmd3 |
          2  |   .4193745   .0447953    -8.14   0.000     .3401585    .5170384
          3  |   .3290229   .0396476    -9.23   0.000     .2598098    .4166743
             |
  weight10kg |   1.042242   .0375734     1.15   0.251     .9711414    1.118549
------------------------------------------------------------------------------
```

Cause-specific hazard regression for death without fracture

```
stset years, failure(status==2)
stcox i.bmd3 weight10kg, nolog  // bmd is defined in 3 quantiles


No. of subjects =         5993                 Number of obs    =      5993
No. of failures =          657
Time at risk    =  30483.46339
                                               LR chi2(3)       =     27.64
Log likelihood  =   -5525.1007                 Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        bmd3 |
          2  |   .9477798   .0894883    -0.57   0.570     .7876585    1.140452
          3  |   .8260441   .0861232    -1.83   0.067     .6733752    1.013326
             |
  weight10kg |    .878259   .0295786    -3.85   0.000     .8221579    .9381883
------------------------------------------------------------------------------
```

Cumulative Incidence Function

Definition: The *cumulative incidence function* for cause k at time t, $F_k(t)$, is the proportion who have developed the k-th event prior to t

The definition above makes adjustment to "# at risk" for censoring (elimination), but not for other competing risks, i.e., for death in the MrOS dataset (accommodation)

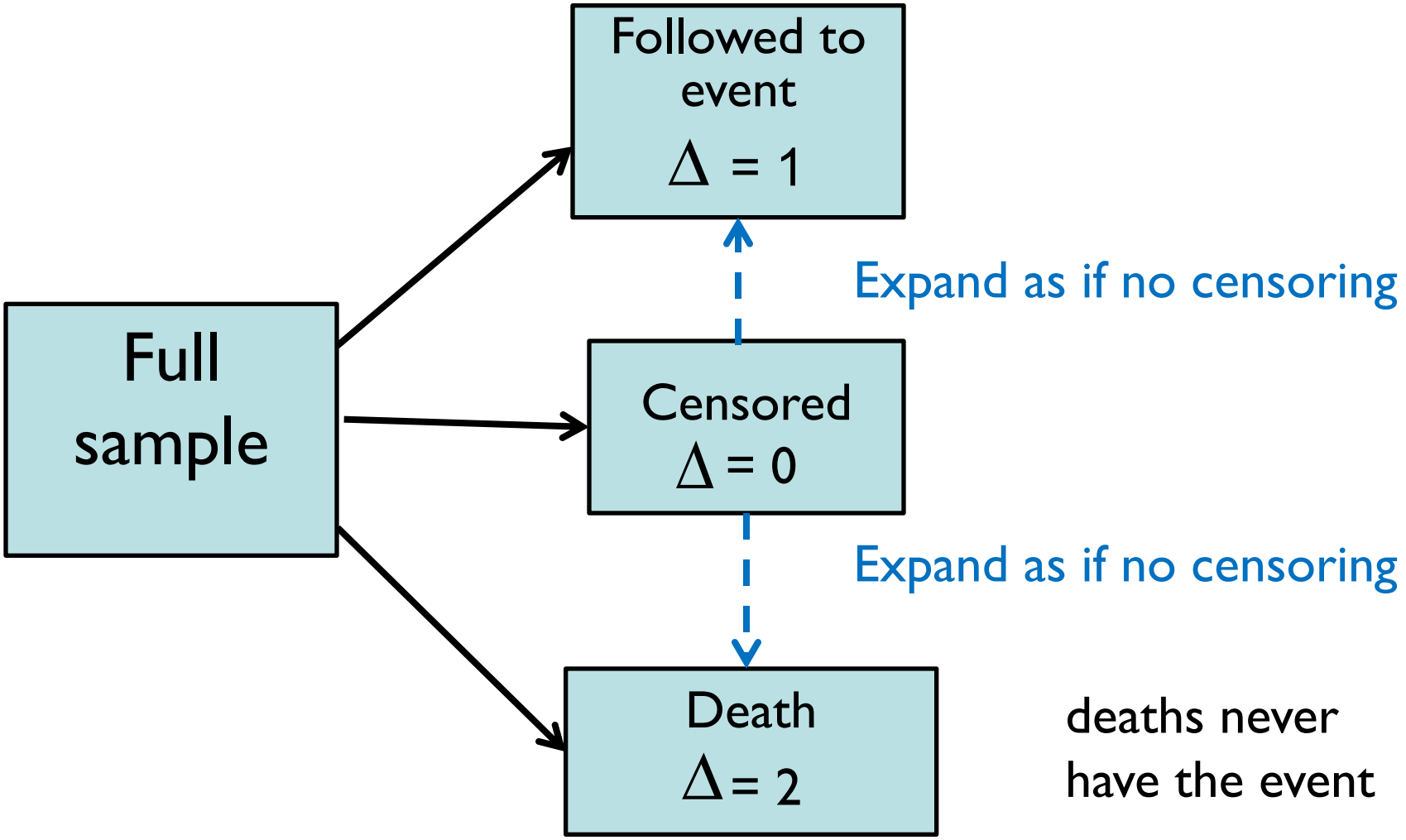
Cumulative Incidence Function

The cumulative incidence function for the k-th event at time *t*, $F_k(t)$, is the probability that a subject experienced k-th event at or before time *t*

$$F_k(t) = F_k(t-1) + \tilde{S}(t-1)h_k(t)$$

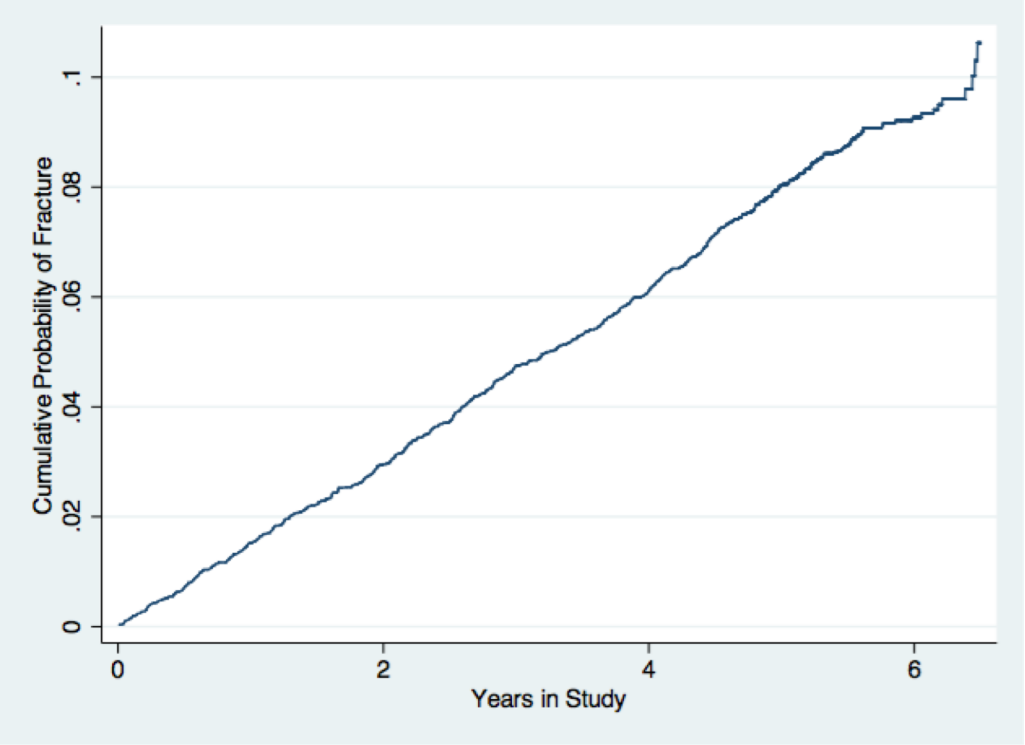
where $\tilde{S}(t-1)$ is the probability of being free of events at time $t-1$, i.e. just prior to time *t*. (In the MrOS data = chance of being alive and unfractured)

Accommodation for competing events plus elimination for censoring



MrOS cumulative incidence function

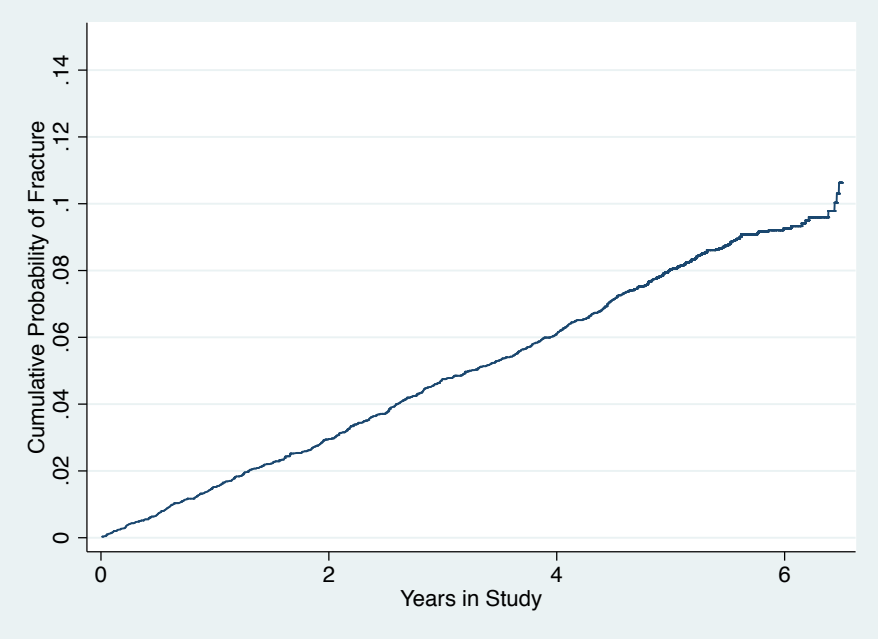
```
clear
use mros.dta
stset years, failure(status==1)   *This specifies event of interest
stcrreg, compete(status==2)       *This specifies competing event
predict cif_fracture, basecif     *Obtain CIF estimate
twoway (line cif_fracture _t if _t < 6.5, sort), ///
ytitle(Cumulative Probability of Fracture)  ///
xtitle(Years in Study)
```



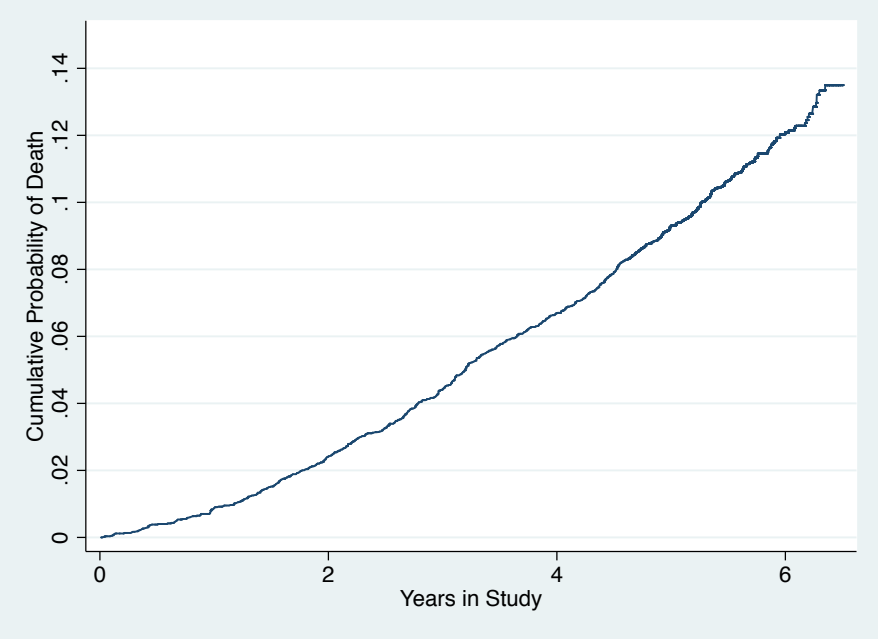
CIF for fracture and death without fracture

```
stset years, failure(status==2)
stcrreg, compete(status==1)
predict cif_death, basecif
twoway (line cif_death _t if _t<6.5, sort), ///
ytitle(Cumulative Probability of Death Without Fracture) ///
xtitle(Years in Study) ylabel(0(0.02).15)
```

CIF of fracture



CIF of death without fracture



Fine-Gray model for cumulative incidence function

- What if BMD is correlated with factors that make death more likely?
- Low BMD might lead to fewer fractures after 2 years because men with low BMD are more likely to die before fracture.
- Solution: compare cumulative incidence function rather than cause-specific hazard.

Fine-Gray model for cumulative incidence function

- Model cumulative incidence function, adapting Cox-type proportional hazard formulation
- Let $f_k(t)$ be the k-th "hazard" where the cohort members who succumb to other competing events are retained in the denominator of their rate (c.f., death)
- $f_k(t|x) = f_{0k}(t) \exp(\beta_{1k}x_1 + \ldots + \beta_{pk}x_p)$

Fine-Gray model for cumulative incidence function

- $f_k(t)$ is often referred to as "subdistribution hazard"
- Maintaining deaths in the risk set of fracture acknowledges someone lost to competing risk (death) will not develop event of interest (fracture) so no extrapolation required -- this is equivalent to assigning the time of fracture for those who died at infinity

MrOS Fine-Gray model for cumulative incidence function

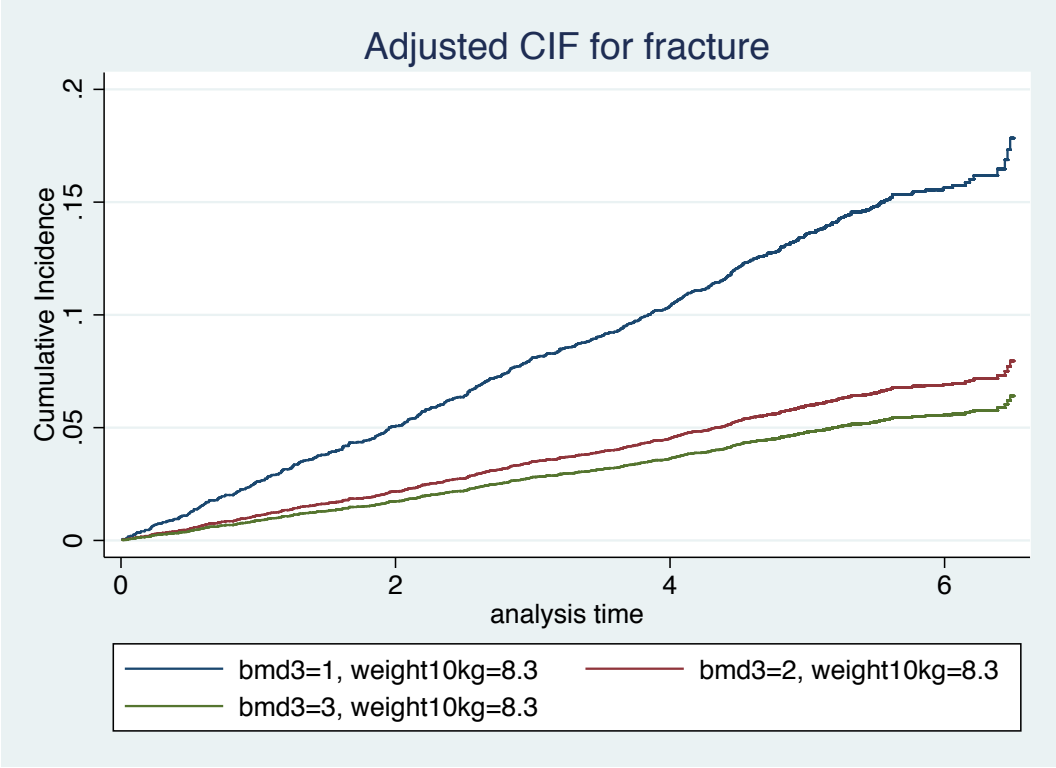
```
use mros.dta
gen weight10kg = weight/10
stset years, failure(status==1)
stcrreg i.bmd3 weight10kg, compete(status==2) // bmd in 3 quantiles

Competing-risks regression                    No. of obs          =      5993
                                              No. of subjects     =      5993
Failure event  : status == 1                  No. failed          =       531
Competing event: status == 2                  No. competing       =       657
                                              No. censored        =      4805

                                              Wald chi2(3)        =    119.64
Log pseudolikelihood = -4472.9261             Prob > chi2         =    0.0000
------------------------------------------------------------------------------
             |               Robust
          _t |        SHR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        bmd3 |
          2  |   .4219663   .0443983    -8.20   0.000     .3433337    .5186079
          3  |   .3369128     .03982    -9.20   0.000     .2672472    .4247387
             |
  weight10kg |   1.047679   .0383331     1.27   0.203      .975178     1.12557
------------------------------------------------------------------------------
```

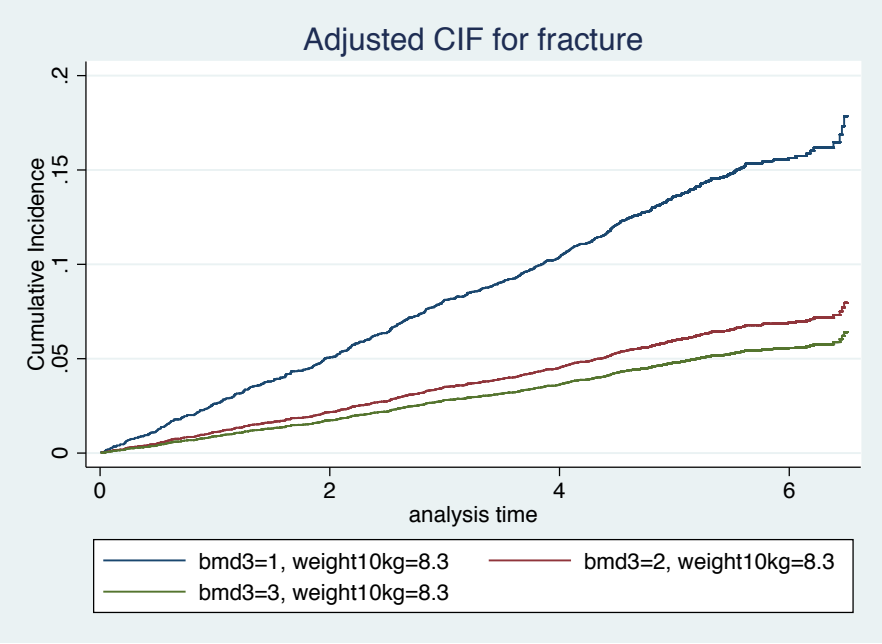
Adjusted CIF curves for fracture

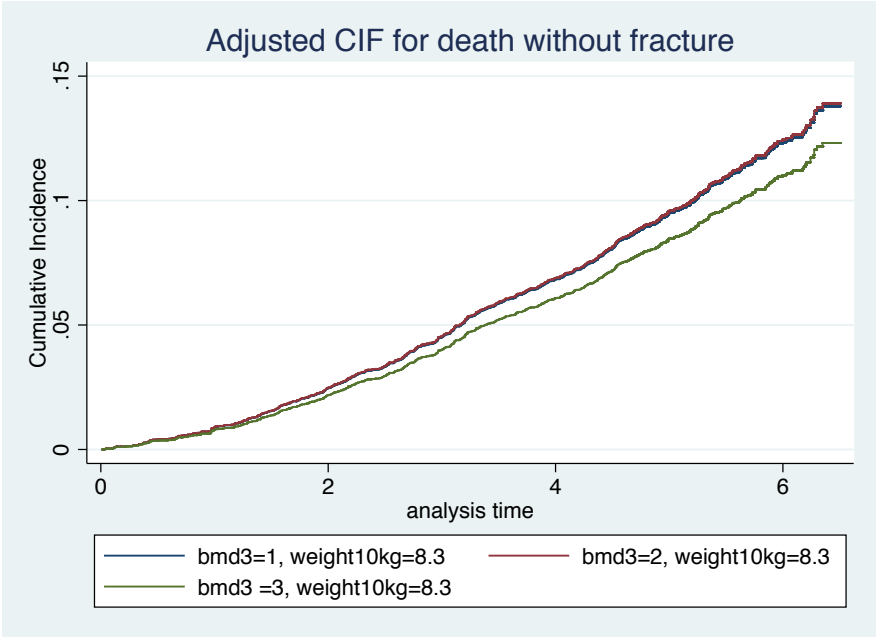
```
stcurve, cif at1(bmd3=1, weight10kg=8.3) at2(bmd3=2, weight10kg=8.3)///
at3(bmd3=3, weight10kg=8.3) range(0 6.5) ///
title("Adjusted CIF for fracture")
```



Adjusted CIF curves for death without fracture

```
stset years, failure(status==2)
stcrreg i.bmd3 weight10kg, compete(status==1)
stcurve, cif at1(bmd3=1, weight10kg=8.3) at2(bmd3=2, weight10kg=8.3)///
at3(bmd3 =3, weight10kg=8.3) range(0 6.5) ///
title("Adjusted CIF for death without fracture")
```





MrOS model comparisons

Cause-specific Cox model

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
bmd3						
2	.4193745	.0447953	-8.14	0.000	.3401585	.5170384
3	.3290229	.0396476	-9.23	0.000	.2598098	.4166743
weight10kg	1.042242	.0375734	1.15	0.251	.9711414	1.118549

Fine-Gray model

_t	SHR	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
bmd3						
2	.4219663	.0443983	-8.20	0.000	.3433337	.5186079
3	.3369128	.03982	-9.20	0.000	.2672472	.4247387
weight10kg	1.047679	.0383331	1.27	0.203	.975178	1.12557

MrOS model comparisons

- MrOS cause-specific hazards and Fine-Gray model results are very similar
- Makes sense: Methods differ based on whether people who die are retained in the risk set – but the risk of death is not large.
- In other cases, covariate effects may of different directions in these two approaches.
- Neither approach is incorrect; all depends on desired interpretation

Competing Risks Summary

- "Deaths" occur due to other causes before event of interest
- Elimination vs. Accommodation
- Cause-specific hazard; cause-specific Cox model (`stcox`); elimination only
- Cumulative incidence function; Fine-Gray model (`stcrreg`); elimination for censoring and accommodation for competing death (by other causes)

Other Survival Topics

- **Interval Censoring**
  - Conventional survival data is right-censored only
  - Often only know event happens in an interval (e.g., between scheduled hospital visits).
  - Regular intervals can use pooled logistic regression (e.g., all patients visit at time 0, 12 months, 24 months and 36 months
  - Non-regular intervals need non-parametric Kaplan-Meier-Turnbull or parametric modeling (i.e. with a model for baseline hazard or survival distribution)
  - Use `intcens` in STATA from SSC for parametric models

    type `ssc install intcens` in STATA then look at:

    `help intcens`

Other Survival Topics

- **Left-Truncation**
  - PBC used time from enrolment for time 0, but makes more sense to use diagnosis time
  - Why LT a problem? subjects with early death less likely to be enrolled – if not accounted for will underestimate early deaths
  - `stset years_since_diag, failure(status) enter(disease_dur)`
    `disease_dur = truncation times (time from Dx to enrollment)`
  - Survival function drops faster early on after accounting for left-truncation
  - See section 6.6.6 in VGSM

Other Survival Topics

- **Clustered data**
  - Dr. McCulloch's lectures have a strong focus on the analysis of clustered data and you will see many examples (but not survival)
  - Clustered survival data consist of e.g., multiple subjects clustered by center, or multiple events (multiple failure times) on a subject (c.f. Dr. McCulloch's lectures)
  - use `shared(cluster_id), cluster(id)` or `vce(cluster id)` in Stata with `stcox`
  - The key is to appropriately set up the data for the type of clustering – ordered vs. non-ordered events, single or multiple event types etc.
  - See

    http://www.stata.com/support/faqs/statistics/multiple-failure-time-data