Survival Analysis IV

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Competing Risks

Competing Risks

- Consider a study looking at time to cardiac arrest in a high risk group comparing treatment and placebo
- But some patients die due to other causes before getting a heart attack and before being censored
- How should we treat those patients?
  - As censored?
  - As events?

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

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

Notation:

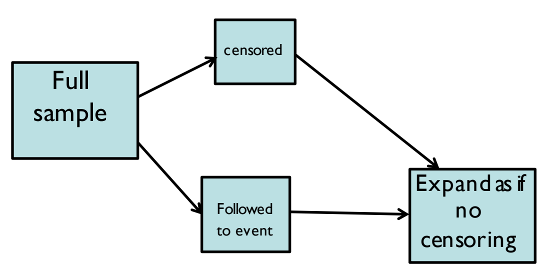
Y: time of first event of any type

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

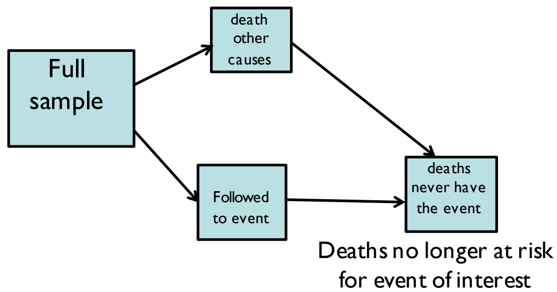
Competing Risks

- **Elimination:** extrapolate to a scenario in which a type of event never happens [e.g., "loss to follow up" or "incomplete follow up"]
- **Accomodation:** acknowledge and allow for the competing risks – treat the competing risk as excluding the patient from having the event of interest [e.g., death]

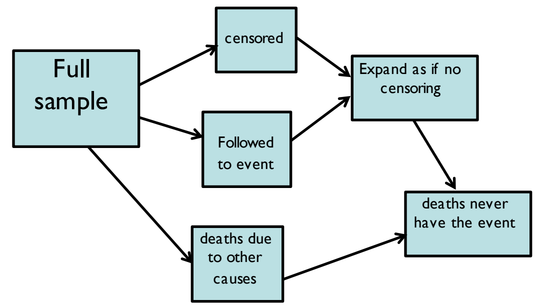
Elimination



Accommodation



Elimination plus Accommodation



MrOS study

- Study predictors of bone fracture and low BMD
- 5993 men over 65 with average 5 year follow-up
- 531 participants fracture, 657 deaths prior to fracture, 4805 alive without fracture
- How well does baseline BMD predict 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

Competing Risk Summaries

- Cause-Specific Hazard Function (c.f., hazard function)
- Cummulative Incidence Function (c.f., survival function)

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.

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

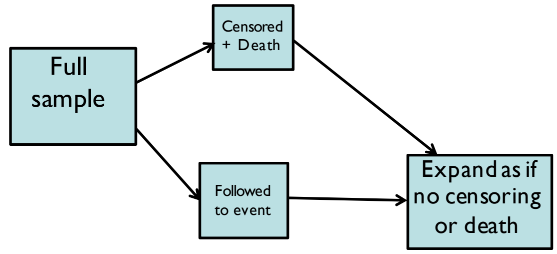
Cause-Specific Hazard Function

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

at risk of k-the event at time t = # alive without fracture immediately prior to time t

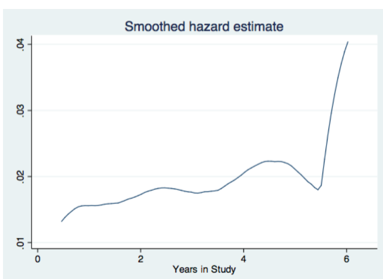
To estimate cause-specific hazard simply set up data as ordinary survival with k-th failure as the only type – all competing causes (even death) treated as censored

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)
```



Cause-Specific Hazard Function

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

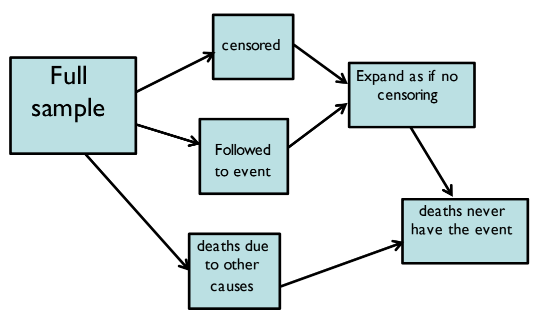
contrast with *cumulative incidence function*…

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)

Elimination plus Accommodation



Cumulative Incidence Function

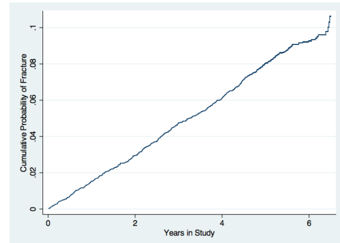
The cumulative incidence function for the k-th event at time t, $F_k(t)$, is

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

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)

MrOS cumulative incidence function

```
clear
use mros.dta
stset years, failure(status==1)
stcrreg , compete(status==2)
predict cif_fracture, basecif
twoway (line cif_fracture _t if _t < 6.5, sort), ///
ytitle(Cumulative Probability of Fracture)  ///
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

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

No. of subjects   =        5993              Number of obs    =      5993
No. of failures   =         531
Time at risk      =   30483.4633 9
                                             LR chi2(3)       =    121.22
Log likelihoo d   =   -4442.290 4            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
      weight |   1.004146     .00362      1.15   0.251      .997076    1.011266
------------------------------------------------------------------------------
```

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 proportional hazard formulation
- Let $f_k(t)$ be the k-th "hazard" where the cohort members who succumb to the competing risk are retained in the denominator of their rate (c.f., death)
- $f_k(t|x) = f_{0k}(t) \exp(\beta_{1k}x_1 + \ldots + \beta_{pk}x_p)$
- Note: Maintaining deaths in the risk set acknowledges someone lost to competing risk will not develop event of interest so no extrapolation required

MrOS Fine-Gray model for cumulative incidence function

```
clear
use mros.dta
stset years, failure(status==1)
stcrreg i.bmd3 weight, 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
```

_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
weight	1.004669	.0036759	1.27	0.203	.9974896	1.011899

MrOS model comparisons

Cause-specific Cox model

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
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2	.4193745	.0447953	-8.14	0.000	.3401585	.5170384
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Fine-Gray model

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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.
- 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)

Finally…

- Dr. McCulloch's first lecture on Repeated Measures next Tuesday
- Check syllabus – all solutions (labs + homeworks) for my lectures should be posted by weekend – let me know if not
- Final project assignments will be in place today