Survival Analysis III

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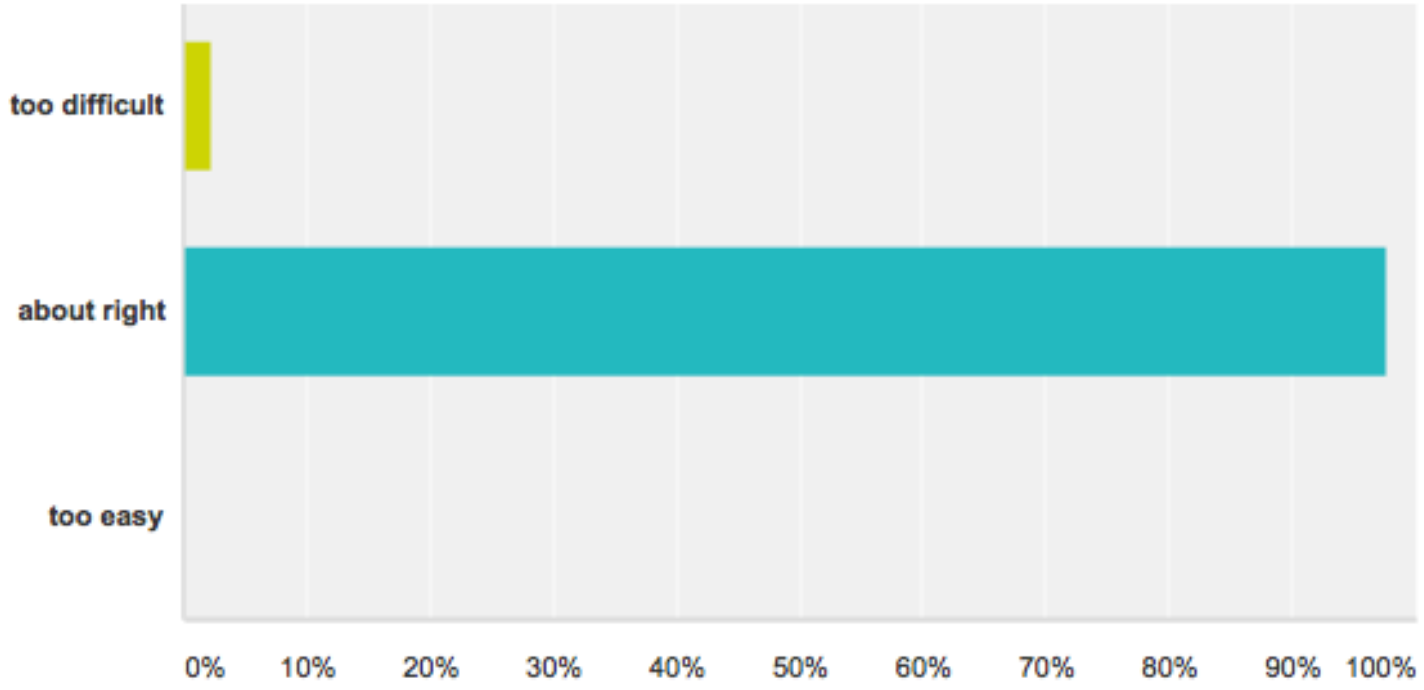
Reading VGSM 6.3 - 6.5

- Homework *#1* due Today in class
- Homework Q/A after class today *12-1*
- Lab 3 on Thursday 10.30 - 6702 & 6704
- Homework #2 due next Tuesday (4/22) in class

Is the level of the survival lectures

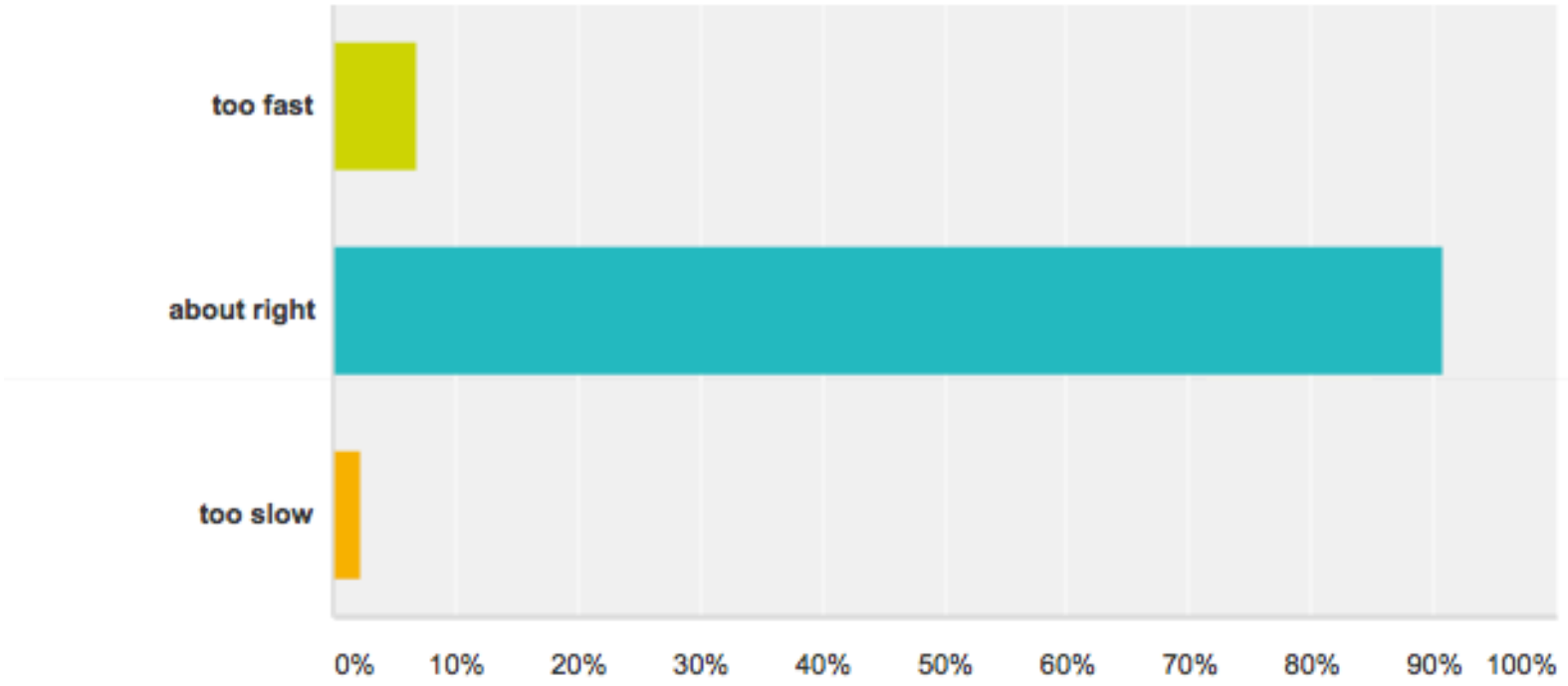
Answered: 44 Skipped: 0



Answer Choices	Responses	
too difficult	**2.27%**	1
about right	**97.73%**	43
too easy	**0.00%**	0
Total Respondents: 44		

Is the pace of the survival lectures

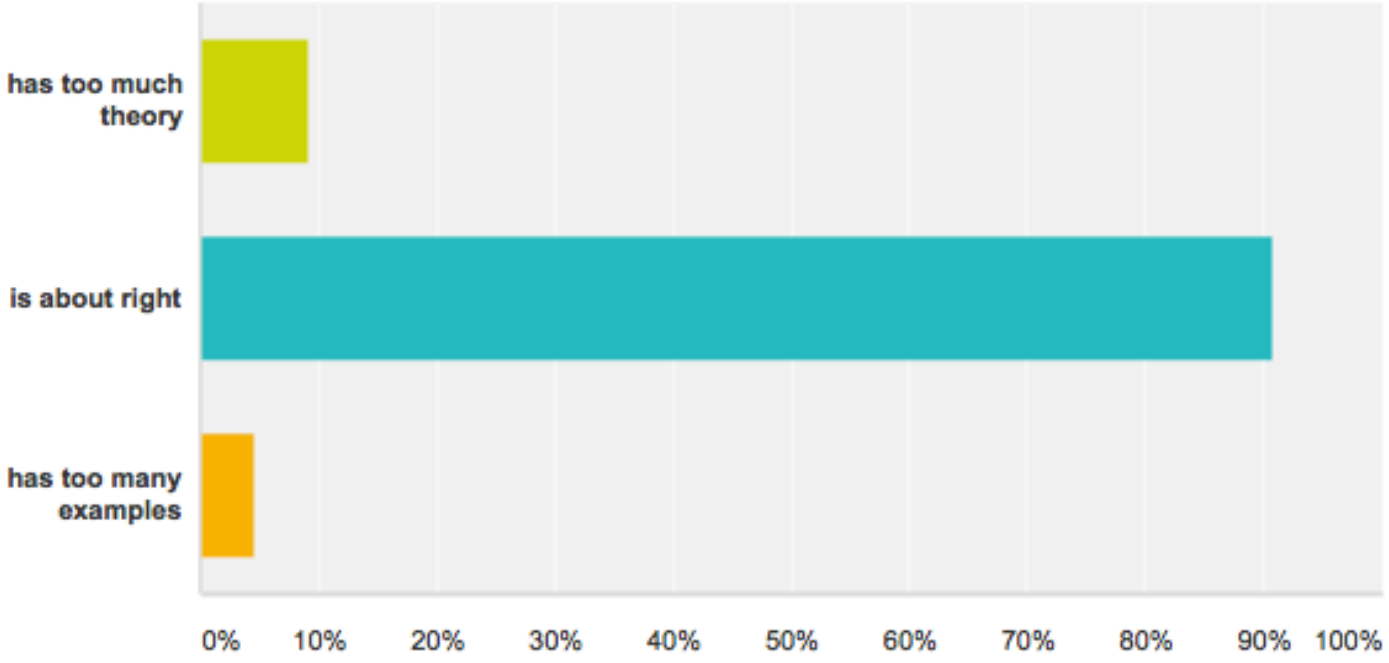
Answered: 44 Skipped: 0



Answer Choices	Responses	
too fast	**6.82%**	3
about right	**90.91%**	40
too slow	**2.27%**	1
Total Respondents: 44		

Do you think the balance between theory and examples

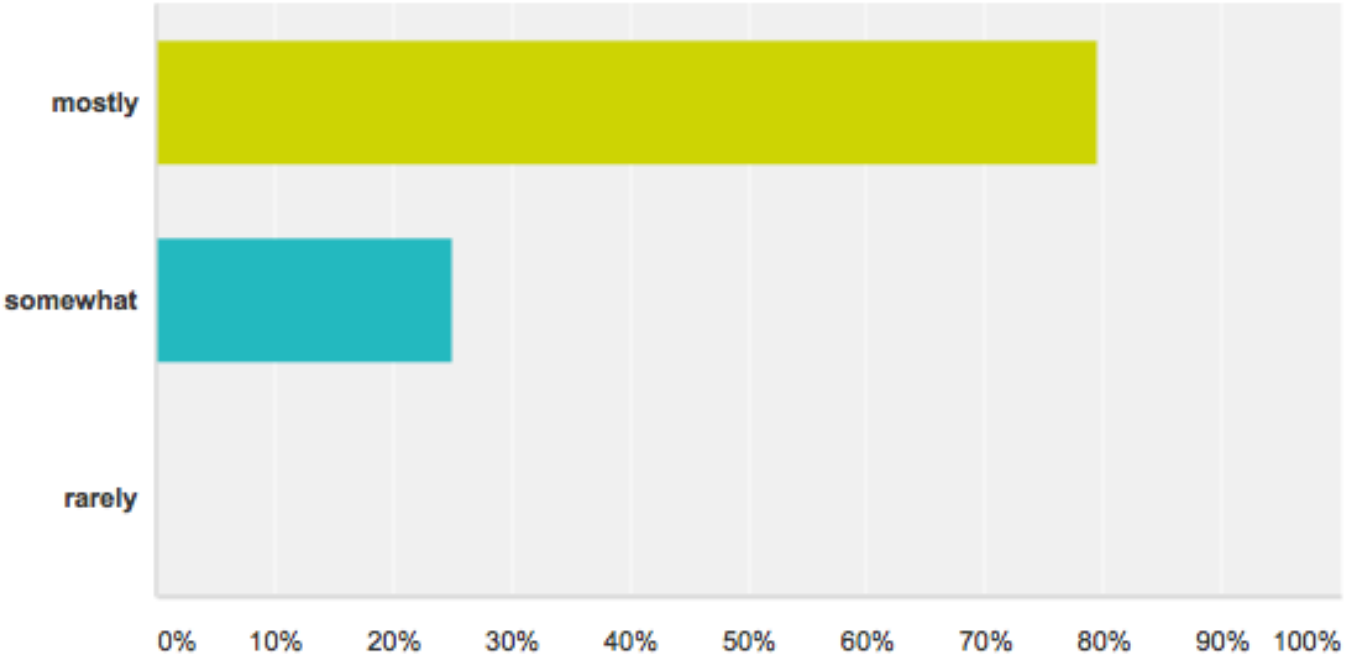
Answered: 44 Skipped: 0



Answer Choices	Responses	
has too much theory	**9.09%**	4
is about right	**90.91%**	40
has too many examples	**4.55%**	2
Total Respondents: 44		

Do you feel that you are following the main concepts

Answered: 44 Skipped: 0



Answer Choices	Responses	
mostly	**79.55%**	35
somewhat	**25.00%**	11
rarely	**0.00%**	0
Total Respondents: 44		

Comments

- Make slides available prior to class
- Post lab solutions faster after class
- Make sections more structured
- Remember to repeat questions for online viewers
- Explain theory covered in more detail – diagrams etc.
- Give more detail/narratives on results interpretation in analysis
- Put more words on the slides
- “I have trouble with the theory. I think it'd be helpful to have a bit more, but I don't think I'd like it! The book does a nice job with supporting theory so maybe not necessary to increase in the lectures.”

So far…

- Survival data and censoring
- Reviewed Kaplan-Meier survival curves and Logrank test
- Hazard function and hazard ratio (HR)
- Proportional hazards model
- Cox Model (no baseline hazard)
- Binary, categorical and continuous predictors
- Wald and likelihood ratio tests
- Zero/infinite HR
- Confounding, mediation, adjusting for other variables
- Interactions and `lincom` statements (danger of extrapolation)

In this lecture
(extensions to the Cox model)

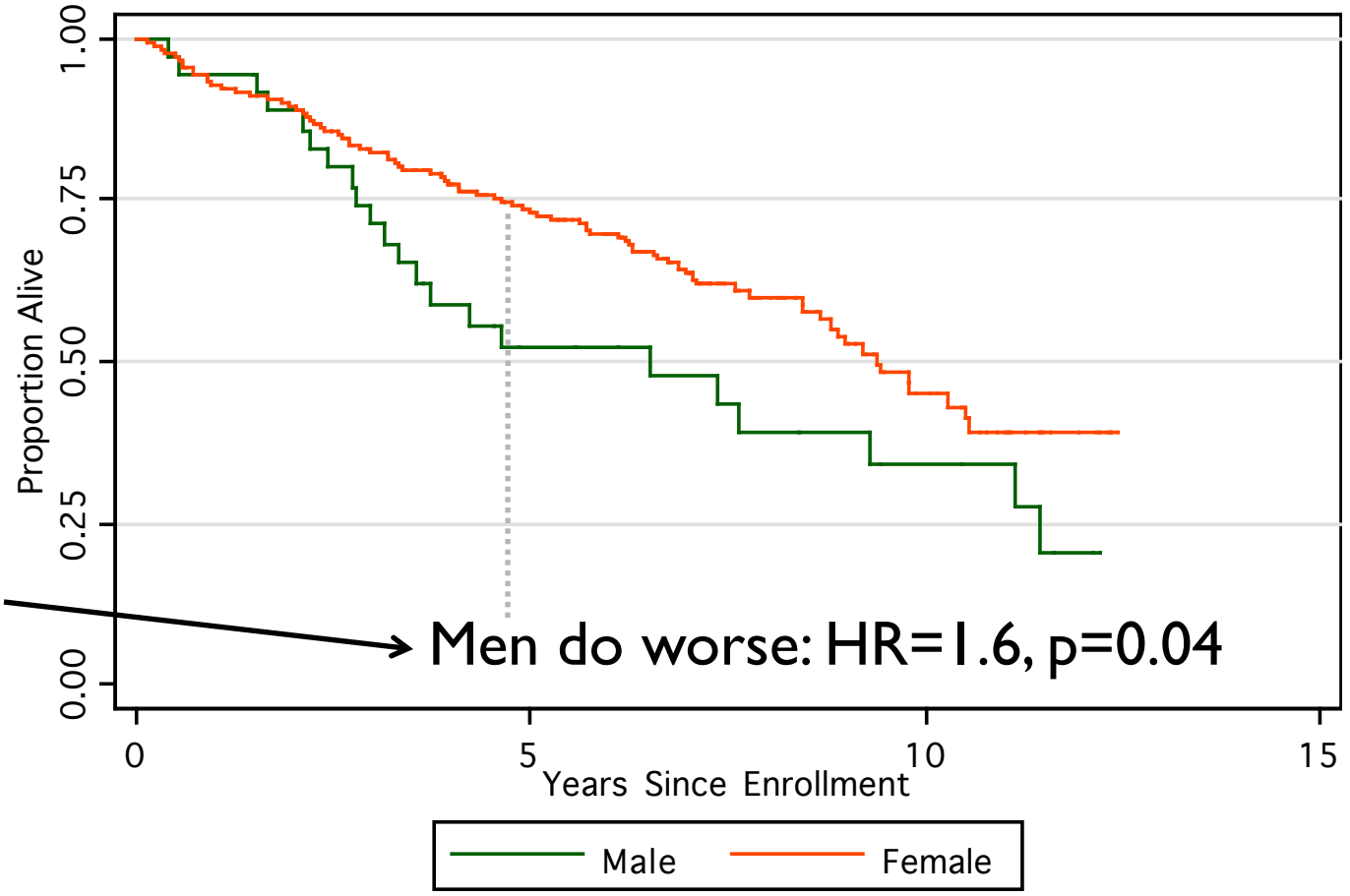
- Adjusted survival curves
- Time-dependent covariates
- Diagnostics (model checking) - proportional hazards?
- Non-proportional Hazards: Stratification
- Non-proportional Hazards: generate time-dependent covariates trick
- Diagnostics (model checking) – linearity of predictors?
- Other methods: Clustered data, Left-Truncation, Interval-censoring

Evaluating Cox model fits: Adjusted Survival Curves

Effect of Sex: PBC data

(unadjusted comparison)

```
use pbc.dat
stset years,failure(status)
sts graph, by(sex)
```

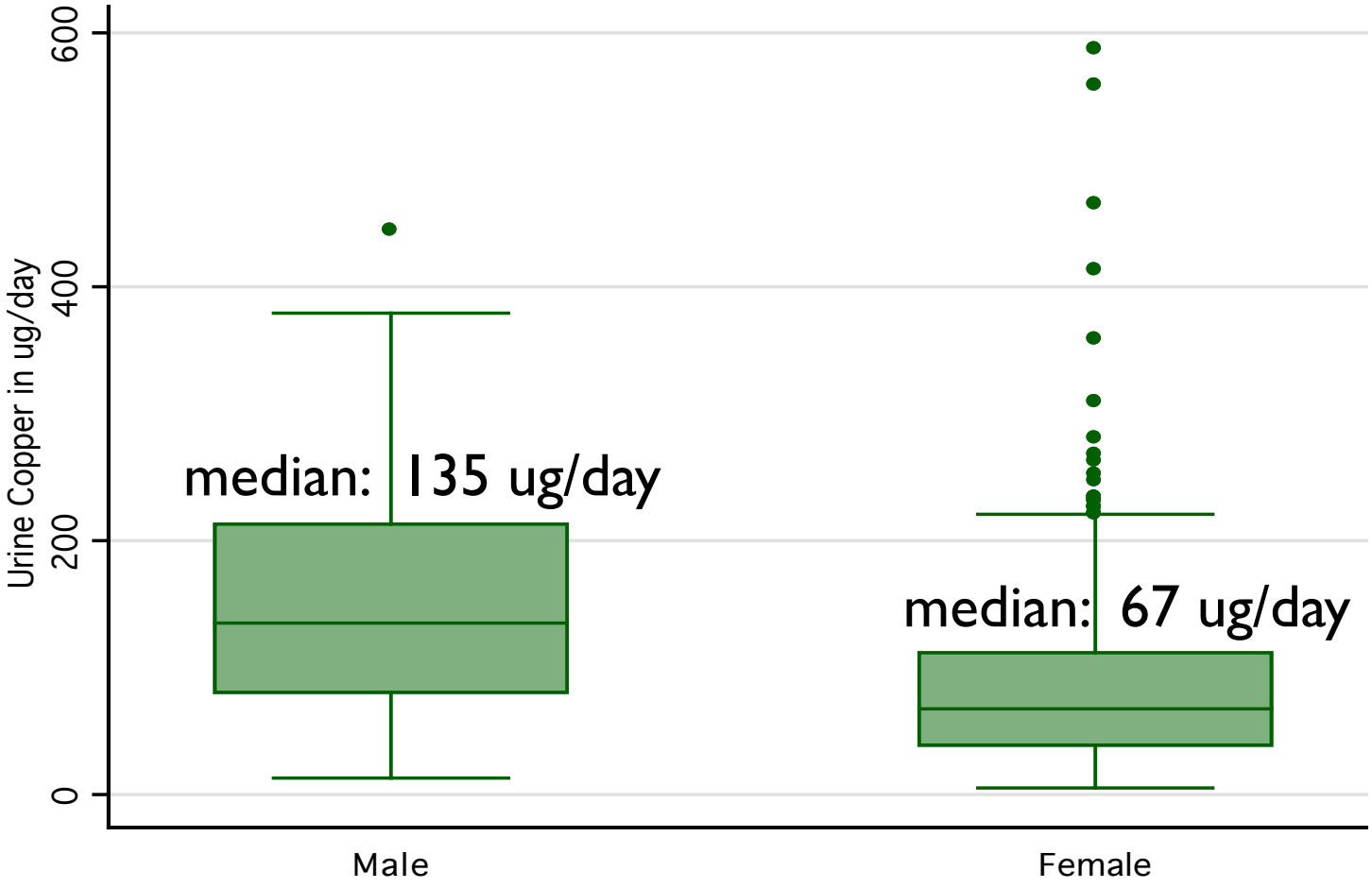



```
stcox sex
```
(Cox model fit)

→ Men do worse: HR=1.6, p=0.04

Men: Higher Copper

```
graph box copper, by(sex)
```



Adjusted Survival Curves

- Would like to visualize the adjusted effects of variables (e.g., controlling for copper)
- Can make survival prediction based on a Cox model
- S(t|x): survivor function (event-free proportion at time t) for someone with predictors x

Under the Cox Model

$$S(t|x) = S_0(t)^{\exp(\beta_1 x_1 + \ldots + \beta_p x_p)}$$

β's are the coefficients from the Cox model

$S_0(t)$:= baseline survivor function

= survivor function when all predictors equal zero

In Cox model we see estimates of $\exp(\beta_p)$

In background, Stata calculates estimates of $S_0(t)$

Adjusted Curve

- Look at effect of x_1 (sex) adjusting for x_2 (copper)
- Create two curves with same value for x_2 *(we are <u>not really adjusting</u> for copper, we <u>are examining</u> the effect of sex with copper held constant)*
- But copper differs by sex! – so should we use sex-specific adjustments?
- So what value for x_2?
  the choice of value will affect the curves
- Let's use overall mean or median

Compare Adjusted Curves 1

```
. stcox sex copper
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   1.171796   .2996835     0.62   0.535     .7098385    1.934391
      copper |   1.006935   .0008328     8.36   0.000     1.005304    1.008569
------------------------------------------------------------------------------
```

```
. stcurve, survival at1(sex=0) at2(sex=1)
```

stcurve: gives predicted curves

survival: graph survival (not hazard default)

at1: (value for curve 1)

at2: (value for curve 2)

Note that the copper default is fixed at overall mean(=97.6)

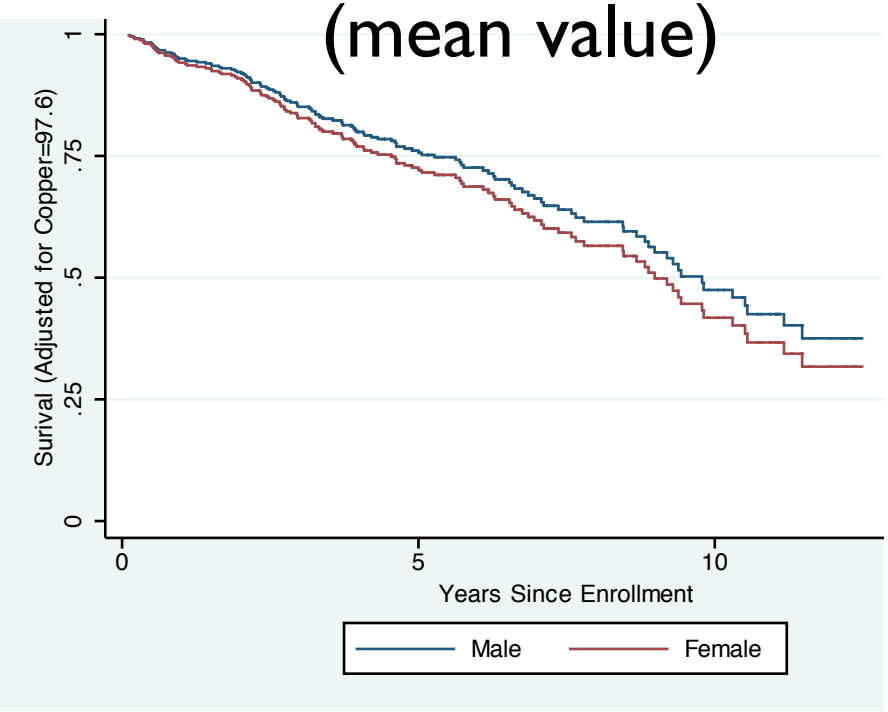
```
. stcurve, survival at1(sex=0 copper=97.6) at2(sex=1 copper=97.6)
```

gives same result

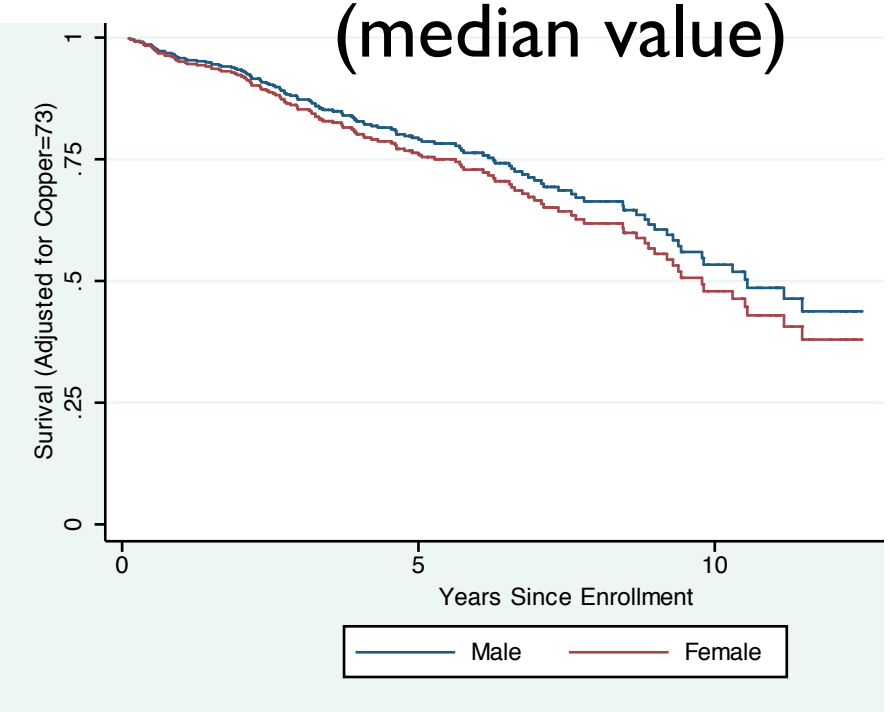
Compare Adjusted Curves 2

```
stcurve, survival at1(sex=0) at2(sex=1)
stcurve, survival at1(sex=0 copper=73) at2(sex=1 copper=73)
```

copper set to 97.6
(mean value)



copper set to 73
(median value)

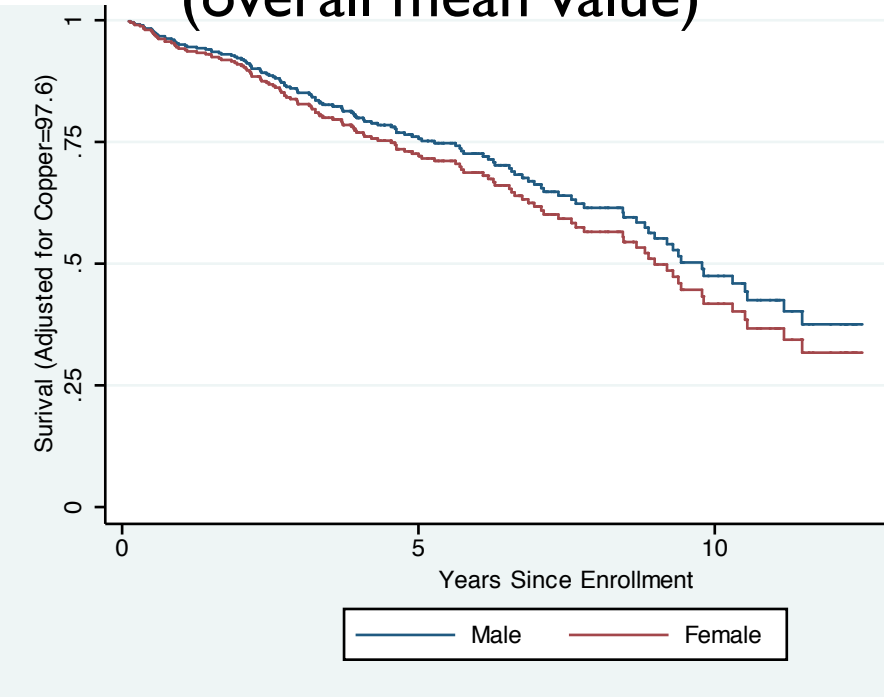


reference value for copper matters

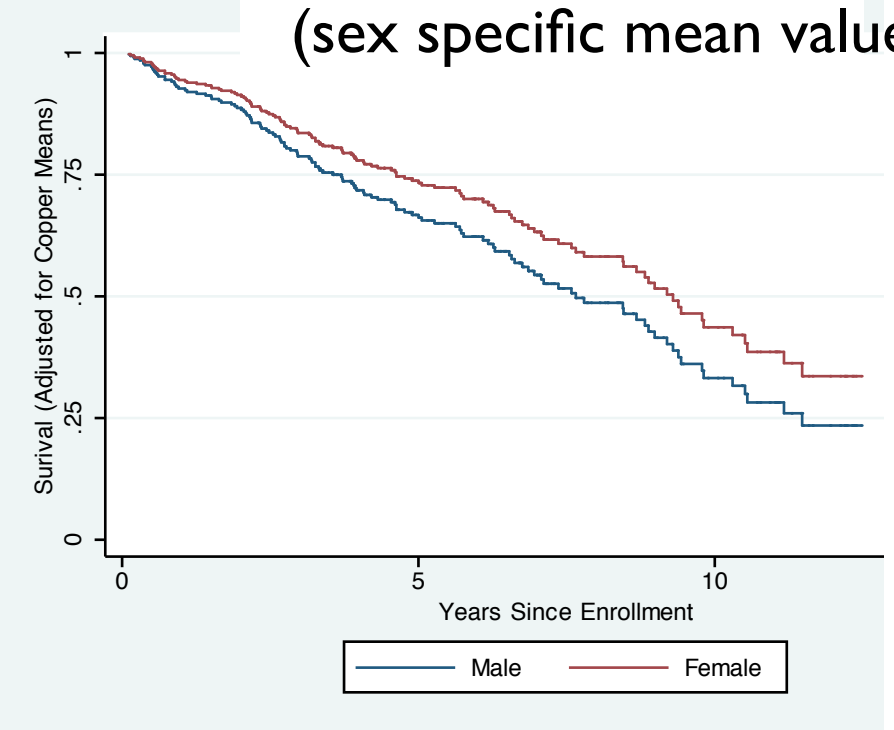
Compare Adjusted Curves 3

```
stcurve, survival at1(sex=0) at2(sex=1)
stcurve, survival at1(sex=0 copper=154) at2(sex=1 copper=90)
```

male and females= 97.6
(overall mean value)



male copper=154, female copper=90
(sex specific mean values)



adjusting for sex differences in copper matters

Adjusted/Predicted Curves

- Can be useful for visualizing effect of predictor
- Must choose reference values for confounders
  - often choose mean for continuous variable
  - most common category for categorical
- `stcurve` is a flexible tool for creating adjusted or predicted survival curves
- Summary: Look at survival curves with `stcurve` while fixing other variables in the model

Time Dependent Covariates

A time-dependent covariate in a Cox model is a predictor whose values may vary with time

… and is measured (or evaluated) at multiple times during the study

Example

- Risk factors for pregnancy in a cohort of HIV infected women in Uganda
- Is the development of pregnancy affected by CD4 cell counts?
- We could consider only baseline CD4 count as a predictor (i.e. CD4 value at study onset)
- *But, CD4 cell count measured throughout the study!*
- Multiple measures of CD4 during study could provide additional prognostic information

Example

E.g., Patient #24901:

CD4 at baseline: 143
CD4 at day 123: 202
CD4 at day 216: 344
CD4 at day 284: 373
Pregnant on day 380

Data

multiple records per subject

	idno	t_from	t_to	cd4	prg
218.	24901	0	123	143	0
219.	24901	123	216	202	0
220.	24901	216	284	344	0
221.	24901	284	380	373	1
229.	25601	0	117	112	0
230.	25601	117	216	304	0
231.	25601	216	293	319	0
232.	25601	293	379	297	0
233.	25601	379	468	302	0
234.	25601	468	560	264	0
235.	25601	560	574	277	0
236.	25601	574	651	277	0
237.	25601	651	738	268	0

- `idno`: subject id #
- `t_from`: start of interval
- `t_to`: end of interval
- `cd4`: cd4 cell count during interval
- `prg`: pregnancy (1 = yes, 0 = no)

Stata syntax to define dataset:

```
stset t_to, failure(prg) id(idno)
```

TDC Cox model

```
gen cd4_50 = cd4/50
stcox cd4_50


No. of subjects =          702                     Number of obs    =      4935
No. of failures =           85
Time at risk    =       448321
                                                    LR chi2(1)       =    129.91
Log likelihood  =   -485.32684                      Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      cd4_50 |   .5456291   .0344751    -9.59   0.000     .4820756    .6175612
------------------------------------------------------------------------------
```

Interpretation: a 50 cell increase in CD4 cell count (at any time point) is associated with a 45% reduction in the rate of pregnancy, 95% CI (-52% to -38%), p < 0.001

A different TDC example…

- Does lung transplant extend life of patients with Cystic Fibrosis?
- Outcome: Time from listing to death or censoring
- Predictor: Received lung transplant (yes or no)

Possible problem?

A different TDC example…

- Does lung transplant extend life of patients with Cystic Fibrosis?
- Outcome: Time from listing to death or censoring
- Predictor: Received lung transplant (yes or no)
- Bias: waiting list mortality!

Short-term survivors unlikely to get a transplant!

Solution

Treat transplant as a time-dependent covariate

$$tx(t) = \begin{cases} 0 & \text{before transplantation} \\ 1 & \text{after transplantation} \end{cases}$$

$$h(t|tx) = \begin{cases} h_0(t) & \text{before transplantation} \\ \exp(\beta)\, h_0(t) & \text{after transplantation} \end{cases}$$

group membership changes over time

Summary

TDC Cox Model

- TD Covariates useful when values of predictors change
- Key is to set up dataset properly
- Straightforward fitting the Cox model
- We will look at another way to use TDC to accommodate non-proportional hazards later…

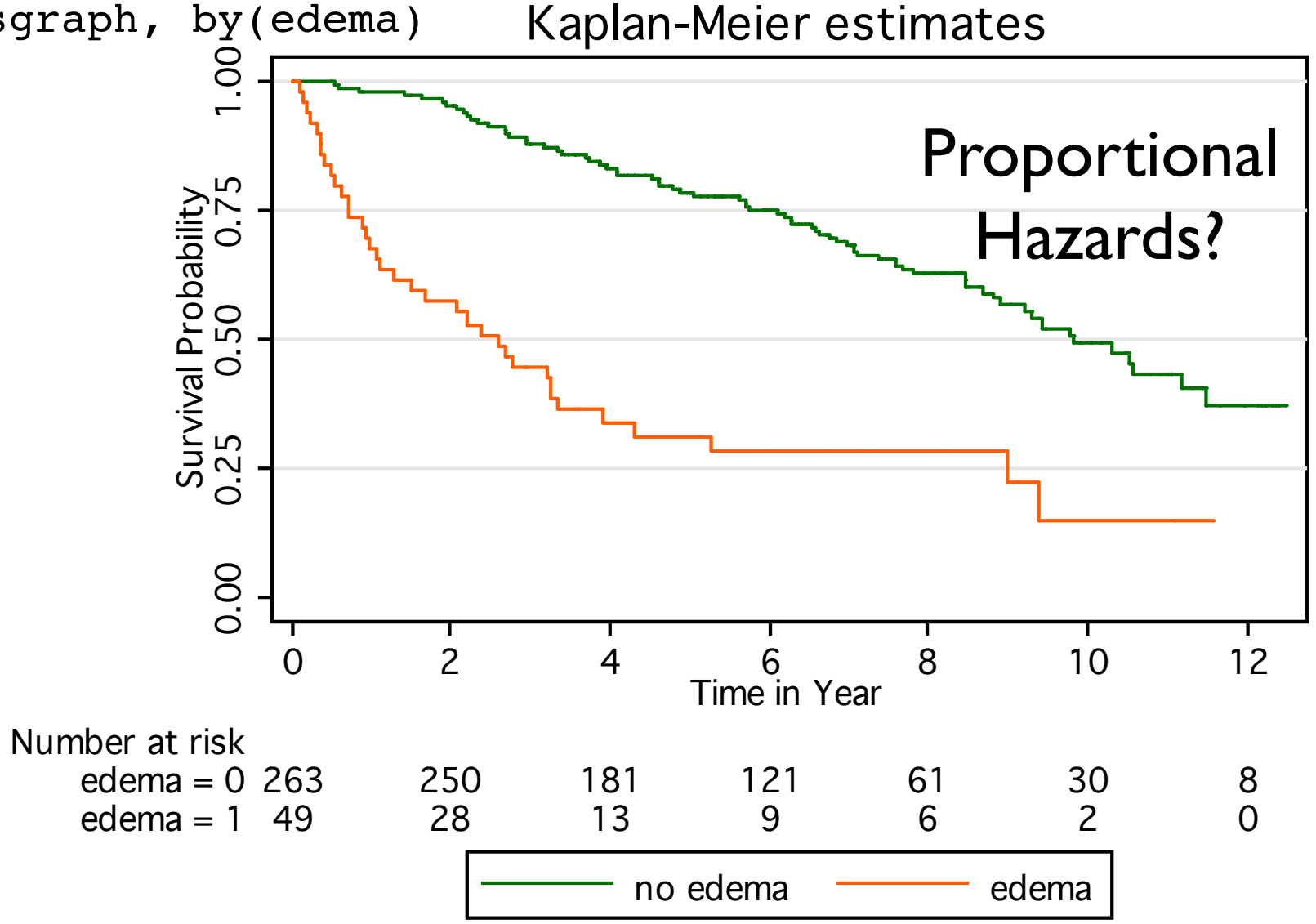
Diagnostics for model checking: *testing the proportional hazards assumption*

“all models are wrong, but some are useful…”

George Box - statistician (1987)

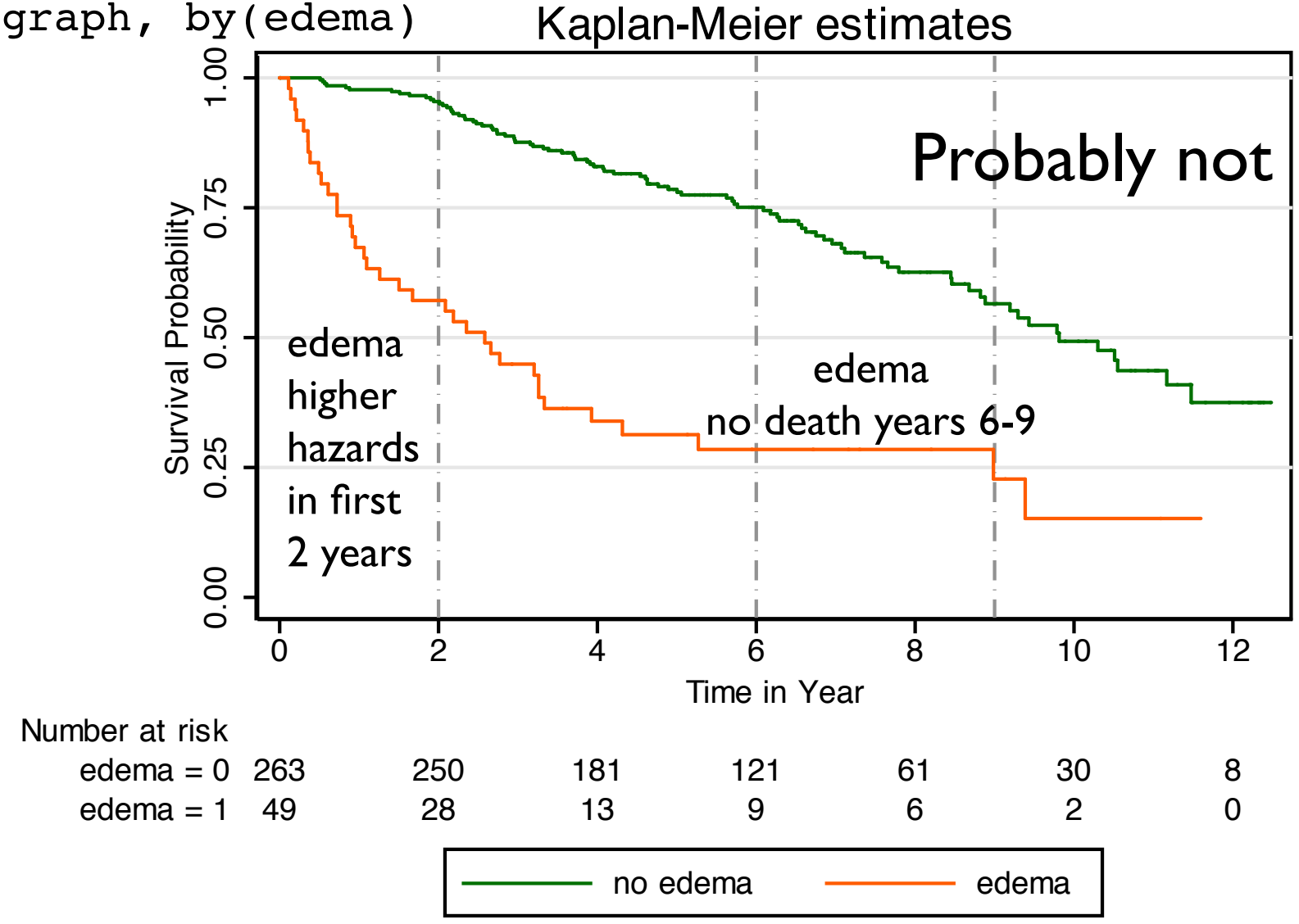
Model Checking PBC Data

```
stsgraph, by(edema)
```



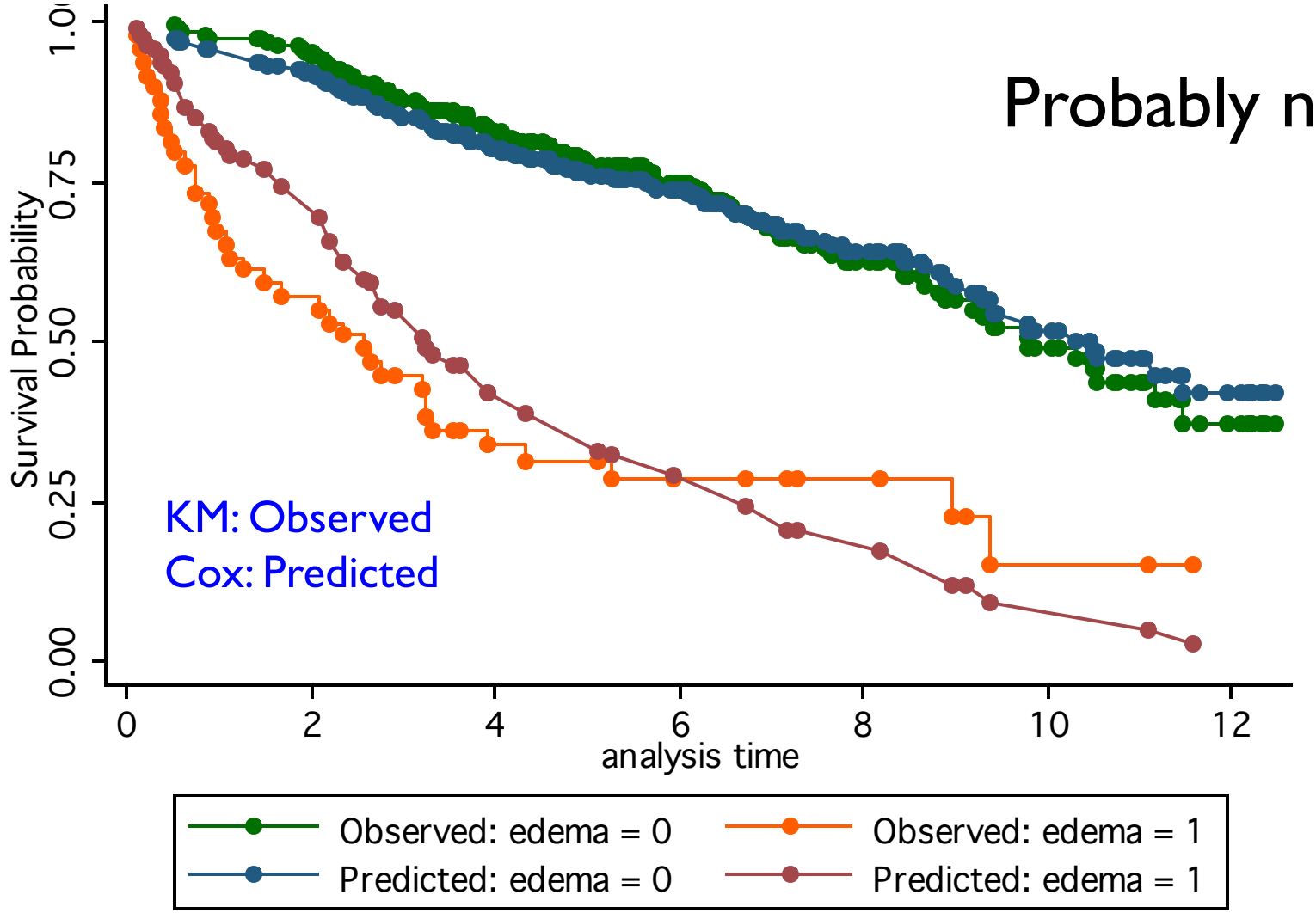
Proportional Hazards?

```
stsgraph, by(edema)
```



Proportional Hazards?

`stcoxkm, by(edema)` – *Kaplan-Meier and predicted survival plot*



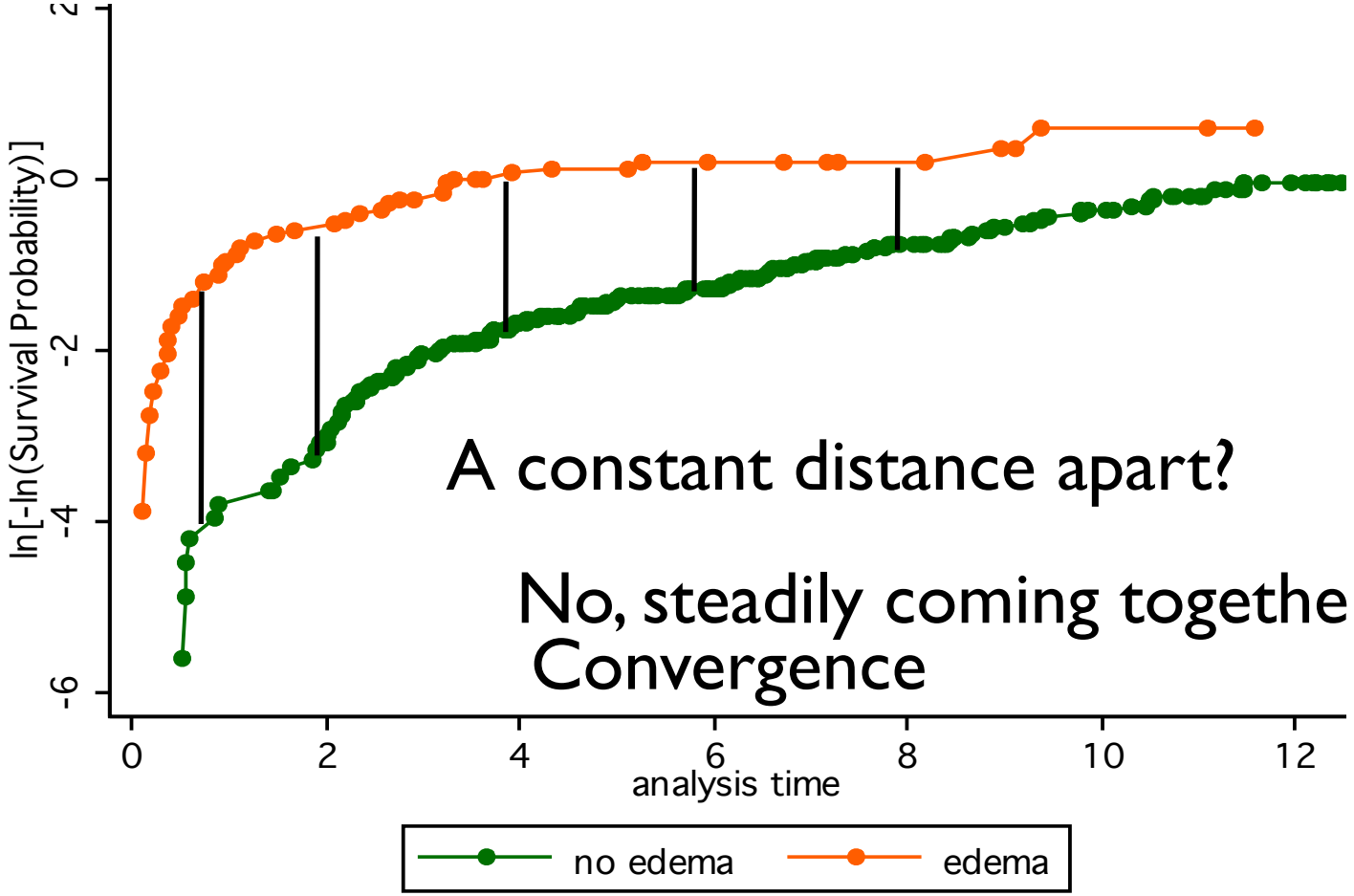
Log minus log plots

Under the Cox model:

- $\log(-\log(S_1(t))) = \beta + \log(-\log(S_0(t)))$
- Estimate survival curves, transform them by: (1) taking log, (2) multiplying by *-1*, then (3) taking log again
- Therefore the curves $\log(-\log(S_1(t)))$ and $\log(-\log(S_0(t)))$ should be a constant distance apart

Log minus log plot: edema

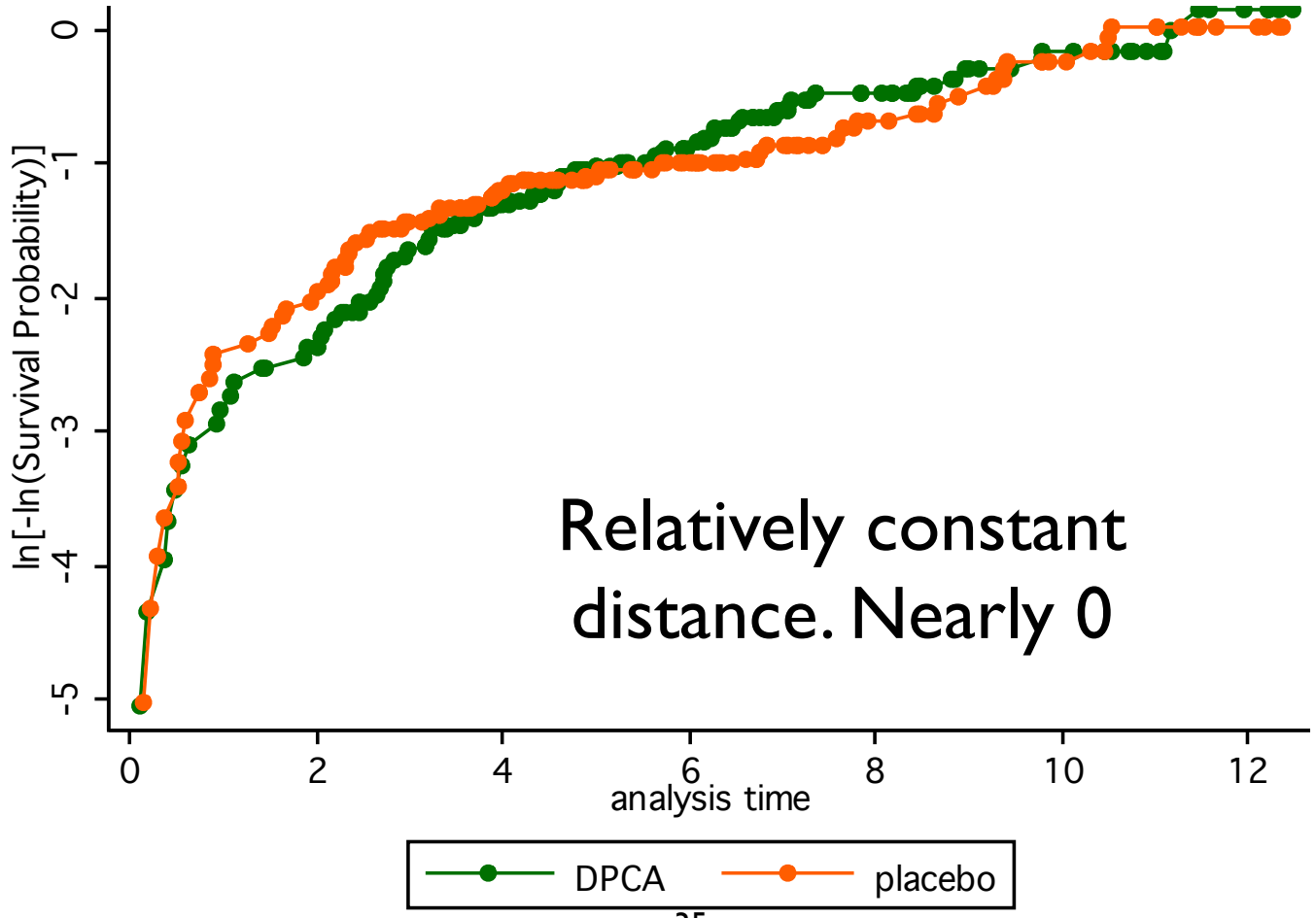
`stphplot, by(edema) nonegative nolntime` –
log minus log curves for `edema`



Log minus log plot: rx

`stphplot, by(rx) nonegative nolntime` –

log minus log curves for `rx`



Interpreting Curves

- Easily calculated (pro)
- Naturally subjective (con)
  - Not so easy to interpret
  - Look for pronounced convergence/divergence, or marked crossing
- Only works for categorical variables (con)
- Multiple crossing is evidence of a lack of overall effect (i.e., difference=0, HR=1)

Smoothed Hazard Ratio

- Possible to use "residuals" to estimate shape of hazard ratio over time
- HR(t): hazard ratio at time t
  - If HR(t) is reasonably constant: prop. hazards
  - If not, gives description of shape of HR
- The method estimates $\log(HR(t)) = \beta(t)$

How does it work?

- Fit Cox model with relevant predictors
- Obtain "scaled Schoenfeld residuals"
  complex formula to generate residuals for each predictor & time point
- LOWESS: smooth residuals vs. time
- Plot the smooth curve estimates of $\beta(t)$
- *Note that estimated curves may change with bandwidth selection*

Stata

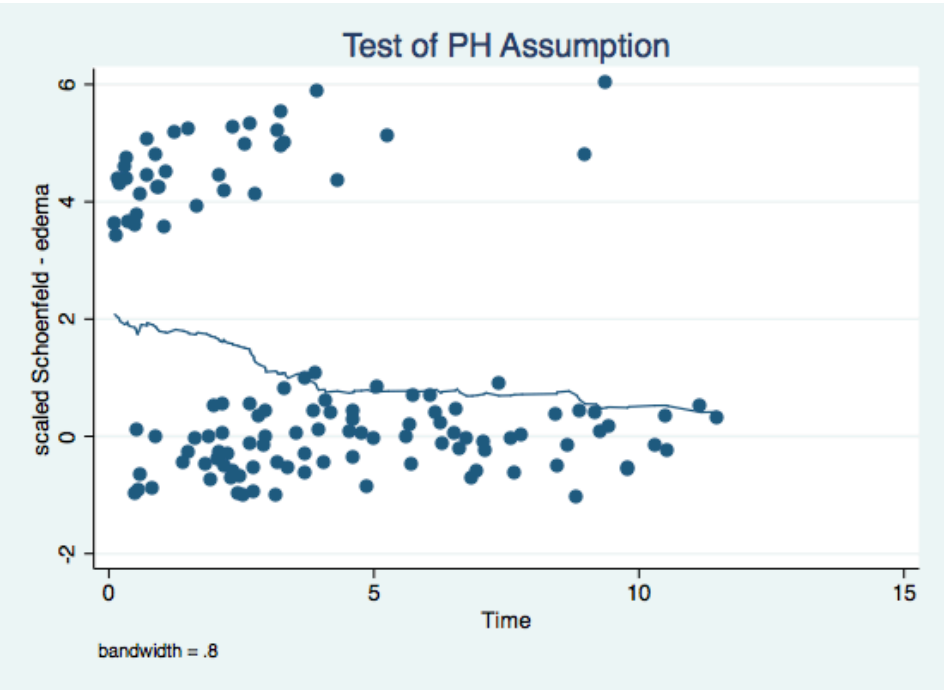
```
gen age10 = age/10

stcox edema age10, scaledsch(r_edema r_age)
```

=> *saves residuals* `r_edema` *for* edema, `r_age` *for* `age10`

```
No. of subjects =          312                     Number of obs    =       312
Log likelihood  =    -614.3788                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       edema |   3.471158   .7099928     6.08   0.000     2.324711    5.182981
       age10 |   1.355471   .1166134     3.54   0.000     1.145143    1.604429
------------------------------------------------------------------------------
```

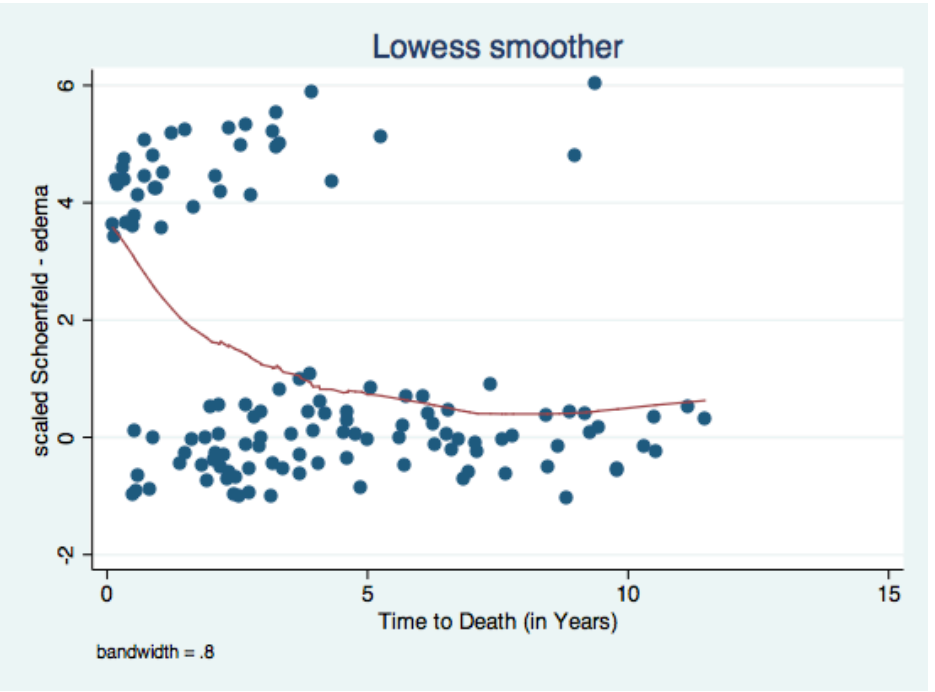
β(t) for edema

`estat phtest, plot(edema)`



running mean smoother `r_edema` *vs.* `time` *to estimate* β(t)

`lowess r_edema years`

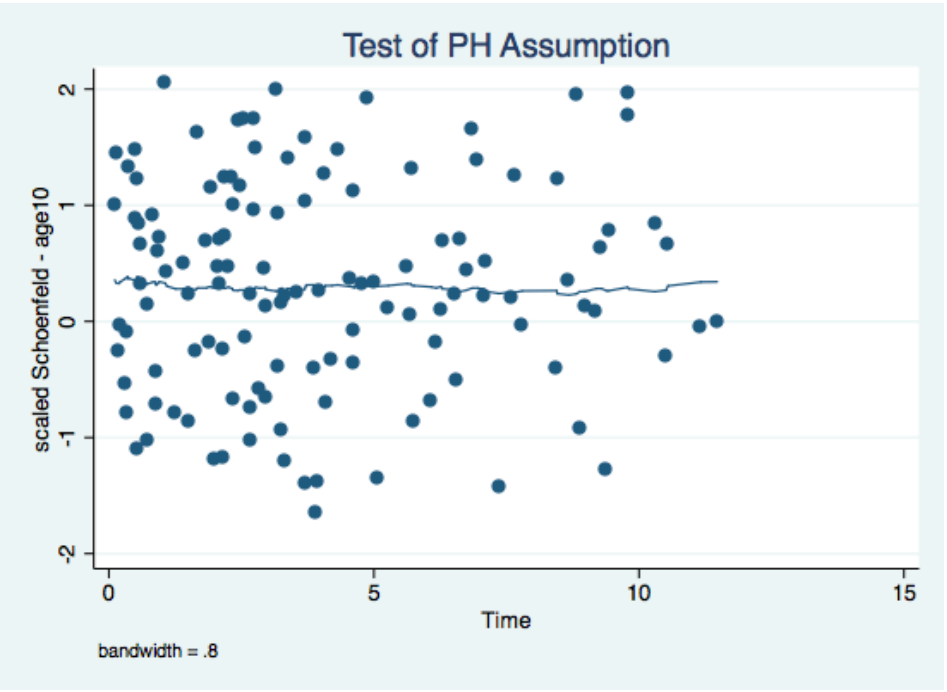


lowess smoother `r_edema` *vs.* `time` *to estimate* β(t)

flat line? *line is not flat, HR is not constant*

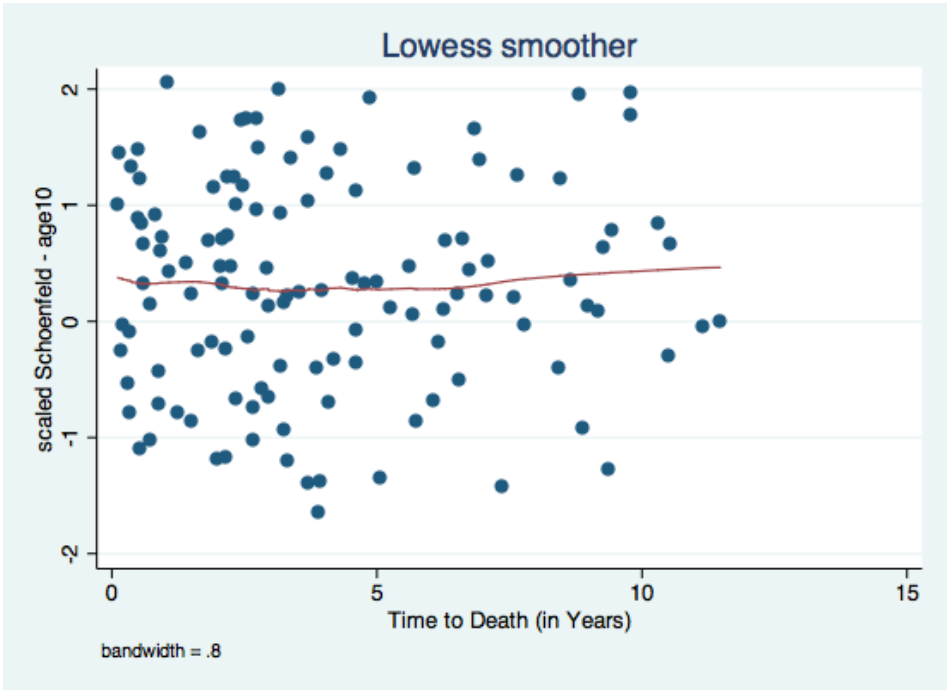
β(t) for age10

`estat phtest, plot(age10)`



running mean smoother `r_age` *vs.* `time` *to estimate* β(t)

`lowess r_age years`



lowess smoother `r_age` *vs.* `time` *to estimate* β(t)

flat line? *line is approximately flat, HR is relatively constant*

Smoothing Hazard Ratio

- Present the smoothed curves as a summary
- Augment it with the table to explain the HR
- Get those values by typing

```
lowess r_edema years, gen(smloghr) nogr
gen smhr=exp(smloghr)
sort years
list years sm* if status==1
```

Lowess $\beta(t)$ values for edema

Years	Log HR	HR
1	2.5	12.2
2	1.6	5.1
4	0.86	2.4
6	0.58	1.8

Test of Proportional Hazards

- Null hypothesis: Hazards are proportional
  i.e., $\beta(t)$ is constant over time
  i.e., no association between residuals & time

- Alternative: Hazards are not proportional
  i.e., $\beta(t)$ changes with time
  i.e., association between residuals & time

Idea is to look at correlation between residuals and time?

Schoenfeld Test

- A test for non-proportional hazards:
  correlation between residual and time

```
stcox edema age10
  estat phtest, detail
```

- Small p-value means
  proportional hazards is rejected –
  the proportional hazards assumption can be shown false

Schoenfeld Test

```
stcox edema age10
estat phtest, detail
```

```
   Test of proportional-hazards assumption

        Time:  Time
        ----------------------------------------------------------------
                    |       rho             chi2       df       Prob>chi2
        ------------+---------------------------------------------------
        edema       |     -0.33749         13.09        1          0.0003
        age10       |      0.01747          0.03        1          0.8540
        ------------+---------------------------------------------------
        global test |                       13.52        2          0.0012
        ----------------------------------------------------------------
```

rho is correlation between residuals and time

We see that edema is significant = *non-proportional hazards*

Scaled Schoenfeld Residuals (plot & test)

- Technical/subjective, so hard to explain (con)
- Poor for multilevel categorical variables
  would need a plot for each level of category (con)
- Handles continuous variables well (pro)
- Can display effects on HR over time
- Note that different time-scaling functions can be used with `estat phtest` - can be important if there are outliers

Graphs vs. Tests

- Graphs and tests are complementary
- Need to look at whether the graph shows evidence of important violation
- Test helps objective assessment of graph
- However, tests have low power when *n* is small (and "too much" power when *n* is large)
- Graphs can show problem with test
  single outlier can affect test

Handling Non-Proportionality

- Stratification
- Time Dependent Covariates

Dealing with non-proportionality: Stratification

Stratified Cox Model

PBC data

- We have seen that baseline edema does not obey proportional hazards, but age does… so model,
- $h(t|edema=1,age) = h_{01}(t)\ \exp(\beta \times age)$

  $h(t|edema=0,age) = h_{00}(t)\ \exp(\beta \times age)$
- Models two separate baseline reference groups
- Proportional within edema but not across:
  relative effect of a 1-unit change in age on hazard is the same for edema = 1 or edema = 0;
  implicitly assumes no interaction between edema and age

Stratification Approach

- Fit a Cox model with terms for proportional variable and stratify by non-proportional variable

```
stcox age10, strata(edema)
```

(proportional) *(non-proportional)*

- Use adjusted survival curves to present the effect of edema

Stratified Cox Model

- Easily implemented in Stata:
  - Proportional hazards model for `age`
  - Stratified by `edema`

```
. stcox age10, strata(edema)

Stratified Cox regr. -- Breslow method for ties
No. of subjects =          312                     Number of obs    =       312
No. of failures =          125
Time at risk    =  1713.853528
                                                   LR chi2(1)       =     11.60
Log likelihood  =   -546.68714                     Prob > chi2      =    0.0007
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       age10 |   1.342085   .1162448     3.40   0.001     1.132539    1.590402
------------------------------------------------------------------------------
                                                        Stratified by edema
```

No p-value, HR etc. for `edema`

Interpretation

For each 10 years increase in age, there is a 34% increase in the hazard of death after adjusting for edema, 95% CI (13% increase to 59% increase)

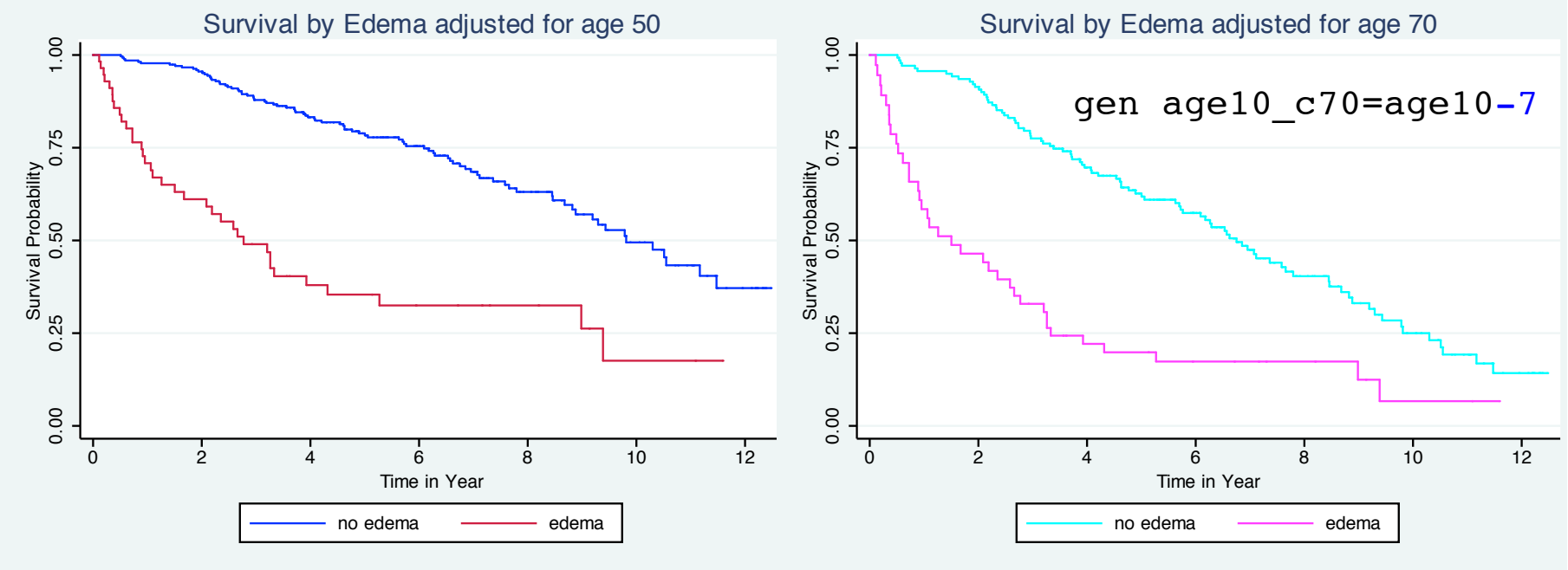
Could mention you did a stratified model in the method section, rather than in the results.

Effect of Edema

- `gen age10_c50=age10-5`

  should center first, graph sets adjusted variables to 0

- `sts graph, by(edema) adjustfor(age10_c50)`



effect of edema is fading in time

Stratification Pros/Cons

- Fairly simple and non-technical approach
- What if the non-proportional variable is continuous?
- What if more than one non-proportional variable?

Summary

Stratified Cox Model

- Stratification requires multiple baseline hazards
- Stratification of a continuous variable (e.g., bilirubin) requires cutting it into categories
- Need to be at least 3-5 events per stratum
- Can use stratification as a way to adjust for non-proportional variable or to *avoid* proportional hazard assumption
- Gives no summary of the effect of stratum, but *adjusted survival curves can show strata effects*

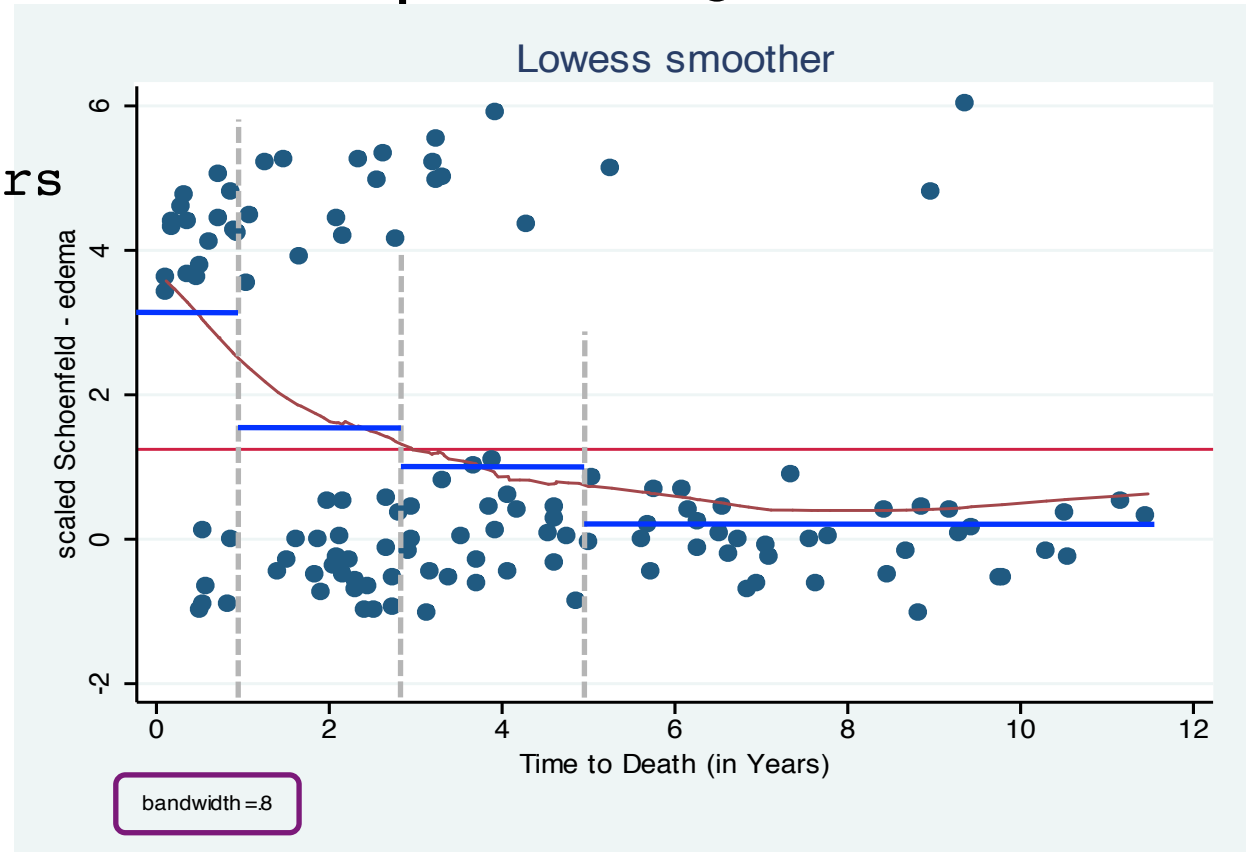
Dealing with non-proportionality: The time-dependent covariates "trick"

Time-Dep Cov Approach

Divide time into **discrete** periods: *e.g., Year 0-1, 1-3, 3-5, 5+*

Edema residuals

```
lowess junk_e years
```



The trick here is that the time interval itself becomes the time varying covariate!

Time-Dep Cov Approach

- Divide time into a series of periods *(e.g., Year 0-1, 1-3, 3-5, 5+)*
- Estimate HR for edema for each period
- Acheived by creating a series of TD covariates:
  `edema01, edema13, edema35, edema5p`
  that separately give the effect of edema in each period

```
stset years, failure(status) id(number)  // generates _t0, _t, _d

stsplit grp, at(1 3 5)  // split time variable (years) at these times into groups ≤ years (grp)
// that is, generate multiple rows for each subject; one for each timepoint up to and including
// the time of censoring or time of death

recode status .=0  // recodes all newly generated rows to "censored" status

gen edema01=edema*(grp==0)  // This set of commands generates 4 separate
gen edema13=edema*(grp==1)  // edema variables specific to each time interval;
gen edema35=edema*(grp==3)  // that is, edemaXX only equals 1 if the patient has edema
gen edema5p=edema*(grp==5)  // AND the dataset row corresponds to period XX
```

TD Cov Set-Up

```
. list number _t0 _t status edema grp edema01 edema13 edema35 edema5p in 1/12, sepby(number)
```

// lists values of the variables: `number _t0 _t status edema grp edema01 edema13 edema 35 edema5p;`
// 'in 1/12' restricts to first 12 rows; 'sepby(number)' draws line between each subject::

	number	_t0	_t	status	edema	grp	edema01	edema13	edema35	edema5p
1.	1	0	1	Censored	1	0	1	0	0	0
2.	1	1	1.0951403	Dead	1	1	0	1	0	0
3.	2	0	1	Censored	0	0	0	0	0	0
4.	2	1	3	Censored	0	1	0	0	0	0
5.	2	3	5	Censored	0	3	0	0	0	0
6.	2	5	12.320329	Censored	0	5	0	0	0	0
7.	3	0	1	Censored	1	0	1	0	0	0
8.	3	1	2.770705	Dead	1	1	0	1	0	0
9.	4	0	1	Censored	1	0	1	0	0	0
10.	4	1	3	Censored	1	1	0	1	0	0
11.	4	3	5	Censored	1	3	0	0	1	0
12.	4	5	5.2703629	Dead	1	5	0	0	0	1

A separate edema variable is set up for each time period so that we can have hazard ratio estimates for edema specific to each time interval!

Output

```
gen age10=age/10
stcox edema?? age10
```

```
No. of subjects =          312                 Number of obs    =      1001
No. of failures =          125
Time at risk    =  1713.853528

                                               LR chi2(5)       =     69.23
Log likelihood  =   -605.36554                 Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     edema01 |   14.45344   6.974774     5.53   0.000     5.613169    37.21639
     edema13 |   3.423855   1.241054     3.40   0.001     1.682588    6.967111
     edema35 |   3.187902   1.495416     2.47   0.013       1.2712    7.994587
     edema5p |   .8742166    .526164    -0.22   0.823     .2687244    2.844009
       age10 |    1.33777   .1153185     3.38   0.001     1.129812    1.584006
------------------------------------------------------------------------------
```

HR declines with time,
does not significantly differ from 1 after year 5

Interpretation

"Adjusted for age, during the first year of follow-up, subjects with edema at baseline have about 14-fold (5.6-37) higher hazard of death. During years 1-3 and 3-5, it is 3.4-fold (1.7, 7.0) and 3.2-fold (1.3, 8.0) higher respectively compared to those with no edema. After year 5, the relative hazard is 0.87 (0.3, 2.8), not statistically significantly different from 1.0."

Output

```
gen age10=age/10
stcox edema?? age10
```

Similar?

```
No. of subjects =          312                 Number of obs    =      1001
No. of failures =          125
Time at risk    =  1713.853528

                                               LR chi2(5)       =     69.23
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       age10 |    1.33777   .1153185     3.38   0.001     1.129812    1.584006
------------------------------------------------------------------------------
```
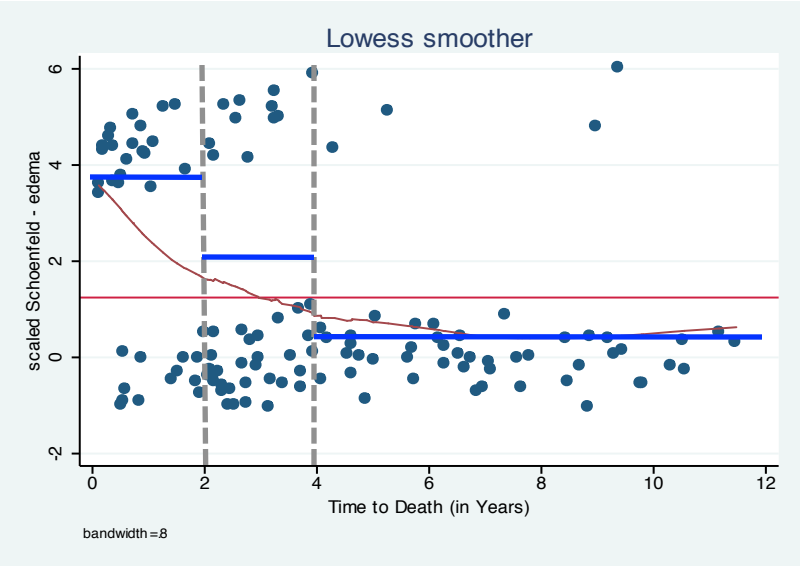

HR declines with time,
does not significantly differ from 1 after year 5

Output

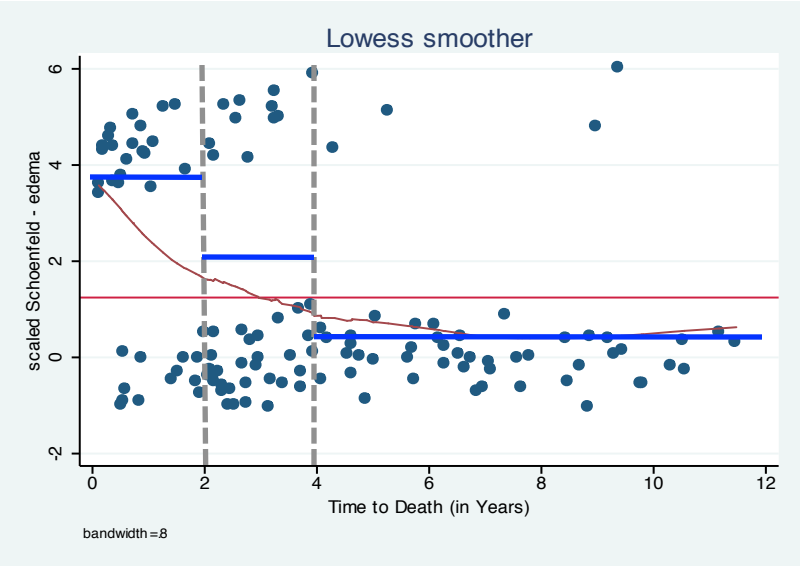
- What if divide time into
  Year 0-2, 2-4, 4+?




```
No. of subjects =          312                     Number of obs    =       784
Log likelihood  =   -604.93786                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     edema02 |   10.54145   3.869923     6.42   0.000     5.133481    21.64657
     edema24 |     3.2131   1.138287     3.29   0.001     1.604626    6.433907
     edema4p |   .9417363   .4928127    -0.11   0.909     .3376709    2.626425
       age10 |   1.342123   .1157712     3.41   0.001      1.13336     1.58934
------------------------------------------------------------------------------
```

Output

- What if divide time into *Year 0-2, 2-4, 4+?*




```
No. of subjects =          312                     Number of obs    =       784
Log likelihood  =   -604.93786                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
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       age10 |   1.342123   .1157712     3.41   0.001      1.13336     1.58934
------------------------------------------------------------------------------
```

TDC Pros/Cons

- Con: Bit of programming to set up
- Con: Somewhat artificial on choice of cut-points
- Pro: Estimates time-varying HRs and 95% CIs
- Pro: Clinicians love cutpoints
  e.g. *can say "edema doesn't matter after 4-5 yrs"*

Overview: Time dependent covariates as a *continuous* interaction with time

- Allows effect of predictor to vary continuously with time
- `stcox` with `tvc()` and maybe `texp(fn(_t))`, or `stplit, at(failures) --` [see Sections 6.4.2.6 and 6.9 of VGSM plus Time varying subsection of `help stcox` and `help tvc_note`: especially see hyperlink to Cox regression with continuous time-varying covariates]

- The continuous interaction with time model is more realistic than splitting at specific times (pro)
- Typically requires transformation so that hazard ratio is a linear (or other "smooth") function of the interaction with time (con)

What about Follow Up Edema Values?

- Recall, edema only codes for baseline edema
- Subjects with edema die off fairly fast
- PBC is a progressive disease
- Subjects are developing edema over time
- If used the yearly information on edema as a TD covariate, the effect may not fade with time

Linearity in Predictors?

continuous predictors

- We considered the proportional hazard assumption
- But what about the linearity of predictors assumption?
- $\log(h(t|x)/h_0(t)) = \beta_1 x_1 + \ldots + \beta_p x_p$

Linearity in Predictors?

continuous predictors

- Possible to use "martingale residuals" to discover a suitable functional form for a *predictor* (possibly adjusted for others)
- Fit Cox model with no predictor, and give a name "*mg_resi*" to the martingale residuals

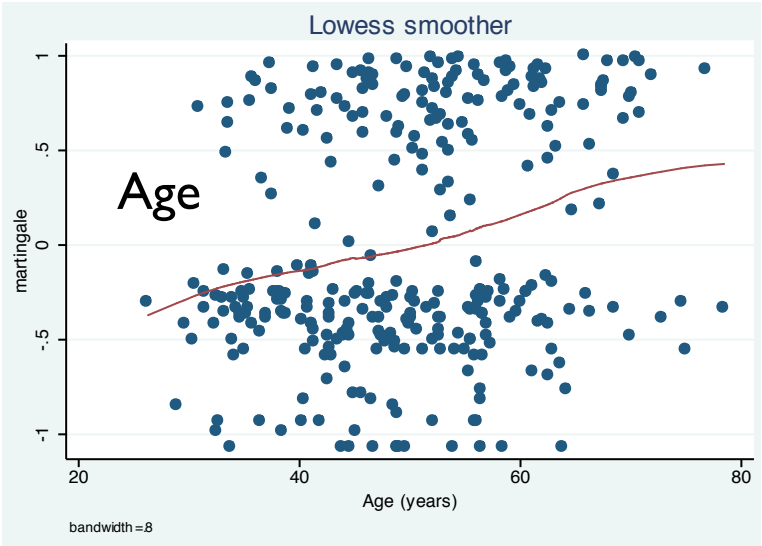
```
. stcox, mgale(mg_resi) estimate
```

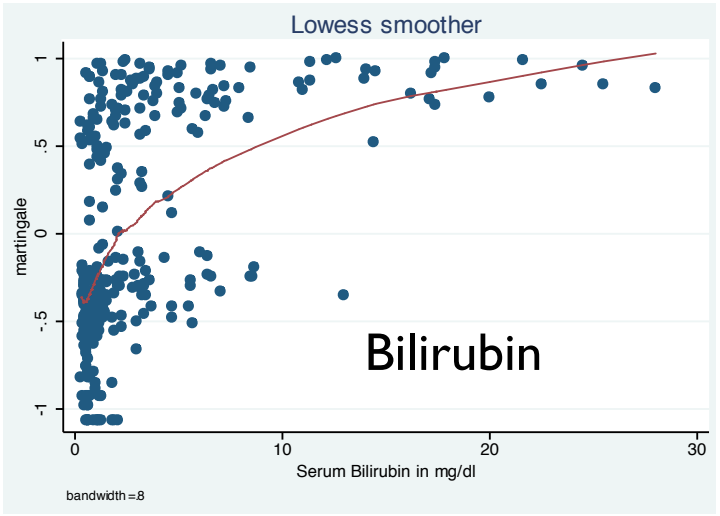
- LOWESS: smooth *mg_resi* vs. *predictor*
- Does it appear to be approx. a straight line?

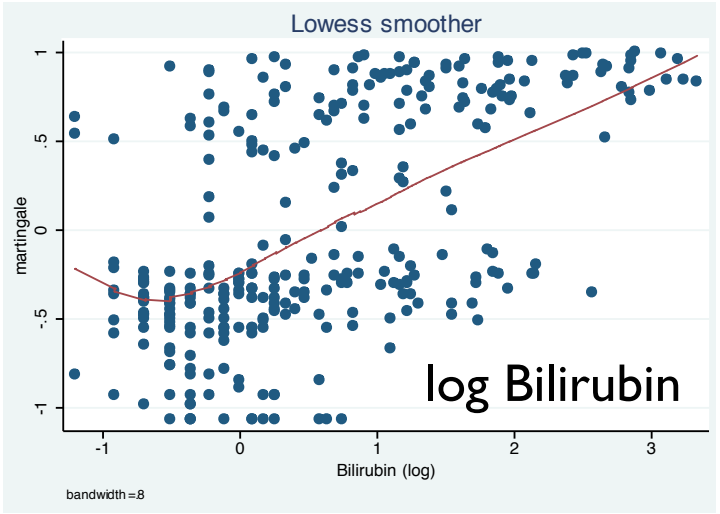
Model Checking: PBC

Linearity in predictors?

```
. use pbc.dta
. stset years, failure(status)
. stcox, mgale(mg_resi) estimate
. lowess mg_resi age
. lowess mg_resi bili
. lowess mg_resi logbili
```







Similar plots can be made while adjusting for other covariates by `stcox covariates, mgale(mg_rescov)` and then, e.g., `lowess mg_rescov age`

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 (see 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

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 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

Summary

- Adjusted survival curves
- Time dependent covariates
- Testing proportional hazards: graphs and test
- Non-proportional hazards solutions

  1) Stratified Cox

  2) Time dependent covariate trick (discrete or continuous)

Other extensions: clustering, competing risks, left-truncation, interval censoring

Don't forget…

- HW 1 discussion will follow now
- Next lecture: "Common Biostatistical Problems" 4/22
- Email HW 2 to Jason Roberts **biostat209.2014.gmail.com** by start of 4/22 lecture.
- HW 2 discussion will follow lecture on 4/22
- **The homework of 4/22 will be due by the lecture on 4/24 -- only a two day window!!!!**