Survival Analysis II

Reading VGSM 6.2.5 - 6.2.13

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- Project description due today
- Hwk #1 due next Tuesday, 4/17/18 – upload via CLE
- Reading for next lecture VGSM 6.3 - 6.5
- Lab. 2 on web site - for this Thursday Rm MH 1400

In this lecture

- Cox model
  - Interpreting Cox model fits
  - Binary, categorical, and continuous predictors
  - Confounding and mediation
  - Interaction terms in the Cox model
- Adjusted survival curves

Survival review: key concepts

- Survival data: right censoring

  Linear/logistic regression sub-optimal

- Aims of a survival analysis

  - Summarize the distribution of survival times
    Tool: Kaplan-Meier estimates (of survival function)
  - Compare survival distributions between groups
    Tool: logrank test
  - Investigate predictors of survival
    Tool: Cox regression model

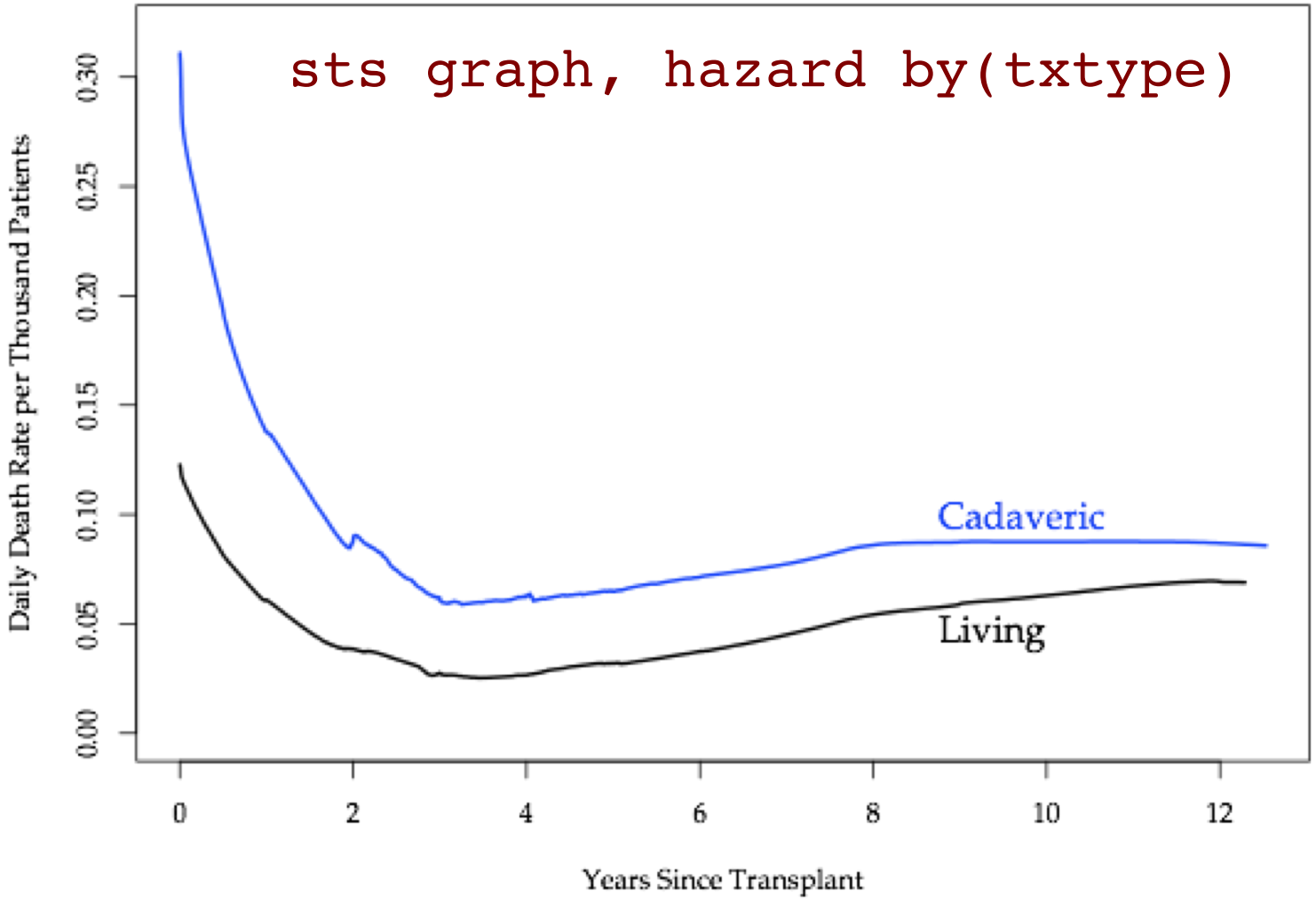
Regression by Outcome

Outcome Data	Regression	Quantity of Interest
Continuous	Linear	Mean
Binary	Logistic	Odds
Survival	Cox	Hazard

Functions for Describing Survival: Hazard Function

- Rate of failure per (small) unit time
- Hazard is like an instantaneous (daily?) death rate:
  h(t) = # die at day t / # followed to t
- More formally: rate of death at time t among those who survive up to t
- Easily estimated for censored data
  (under independent censoring)

Hazard by Type of Tx (UNOS data)



Hazard rates over time

	1000 × Haz Rate		*Relative*
Time	*Cadaveric*	*Living*	*Rate*
3mo	0.235	0.098	2.40
6mo	0.193	0.082	2.36
1yr	0.138	0.061	2.27
2yr	0.088	0.038	2.30
3yr	0.061	0.027	2.25
4yr	0.063	0.026	2.37
5yr	0.065	0.032	2.03

- $h_0(t)$: hazard for living recipients at t (col. 3)
- $h_1(t)$: hazard for cadaveric recipients at t (col. 2)
- $h_1(t)/h_0(t)$: relative short-term risk (col. 4)
  "hazard ratio" at time t

Estimated hazard ratio differs greatly over time?

Hazard Ratio in UNOS Data

- Hazards changed with time
  cadaveric: 0.24 at 3 mos, 0.07 at 5 years
  living: 0.10 at 3 mos, 0.03 at 5 years
- But, their ratio (estimated hazard ratio) didn't vary much: between 2.03 and 2.40
- "Cadaveric recipients have a little over twice the death rate of living recipients"
- Hazard ratio is a useful quantity for discussing predictor effects
- Proportional hazards model: gives predictor effects based on hazards, i.e., regression estimates in terms of hazard ratios.

Proportional Hazards Model

- $x = (x_1, \ldots, x_p)$: the set of predictors
- $h(t|x)$: hazard of someone with predictors x
- $h(t|x) = h_0(t) \exp(\beta_1 x_1 + \ldots + \beta_p x_p)$

  $h(t|x)/h_0(t) = \exp(\beta_1 x_1 + \ldots + \beta_p x_p)$
- $\log(h(t|x)) = \log(h_0(t)) + \beta_1 x_1 + \ldots + \beta_p x_p$

  $\log(h(t|x)/h_0(t)) = \beta_1 x_1 + \ldots + \beta_p x_p$

  because $\log(ab) = \log(a) + \log(b)$
- Formulation is much like logistic regression but change *odds* to *hazards*

Cox Model

- The "baseline" hazard $h_0(t)$ is unspecified; *plays the role of intercept*
- Predictor effects in terms of hazard ratios; *relative rates of failure*
- Key point: don't need to know $h_0(t)$ to understand the effects of predictors
- The effect of one unit increase in predictor x_p is to multiply hazard by $\exp(\beta_p)$ (holding all other predictors constant)….

Binary Predictor (UNOS)

$$x = \begin{cases} 0 & \text{Living} \\ 1 & \text{Cadaveric} \end{cases}$$

$$h(t|x) = h_0(t)\ \exp(\beta x)$$

Binary Predictor (UNOS)

$$x = \begin{cases} 0 & \text{Living} \\ 1 & \text{Cadaveric} \end{cases}$$

$$h(t \mid x) = h_0(t)\exp(\beta x)$$

Hazard in cadaveric group

$$h(t \mid x=1) = h_0(t)\exp(\beta \times 1)$$

versus hazard in living donor group

$$h(t \mid x=0) = h_0(t)\exp(\beta \times 0)$$

$$\text{Ratio} = \frac{h_0(t)\exp(\beta)}{h_0(t)\exp(0)} = \exp(\beta)$$

$\exp(0) = 1$

+1 unit change in x_p

$$h(t|x) = h_0(t)\exp(\beta_1 x_1 + \ldots + \beta_p V) \qquad x_p = V$$

versus

$$h(t|x) = h_0(t)\exp(\beta_1 x_1 + \ldots + \beta_p (V+1)) \qquad x_p = V+1$$

$$\text{Ratio} = \frac{h_0(t)\exp(\beta_1 x_1 + \ldots + \beta_p (V+1))}{h_0(t)\exp(\beta_1 x_1 + \ldots + \beta_p V)}$$

+1 unit change in x_p

$$\text{Ratio} = \frac{\cancel{h_0(t)}\exp(\beta_1 x_1 + \ldots + \beta_p(V+1))}{\cancel{h_0(t)}\exp(\beta_1 x_1 + \ldots + \beta_p V)}$$

$$= \frac{\exp(\beta_1 x_1 + \ldots + \beta_p (V+1))}{\exp(\beta_1 x_1 + \ldots + \beta_p V)}$$

Ratio does not depend on t !

+1 unit change in x_p

$$\text{Ratio} = \frac{\exp(\beta_1 x_1 + \ldots + \beta_p (V+1))}{\exp(\beta_1 x_1 + \ldots + \beta_p V)}$$

$$= \exp(\beta_1 x_1 + \ldots + \beta_p (V+1) - (\beta_1 x_1 + \ldots + \beta_p V))$$

because exp(a)/exp(b) = exp(a-b)

$$= \exp(\beta_p (V+1) - \beta_p V)$$ b/c same other predictors

$$= \exp(\beta_p)$$ b/c $\beta_p V$ terms cancel

Hazard Ratio (HR)

- β is the regression coefficient
- If a predictor variable has no effect then $\beta=0$
- HR for a unit increase in a predictor is $\exp(\beta)$ -- if predictor has no effect then $\exp(\beta) = \exp(0) = 1$
- Can readily switch from summarizing models in terms of coefficients, β, or in terms of hazard ratios, $\exp(\beta)$
  - HR's work better for interpretation, but math simpler based on coefficients

`Stata` Command

- First use the command `stset` to declare the data as survival
- Then fit Cox model with

`stcox` *predictorlist*

Stata Output

```
. stcox txtype

No. of subjects =         9750                 Number of obs    =      9750
No. of failures =          438
Time at risk    =  38236.09865

                                               LR chi2(1)       =     49.23
Log likelihood  =   -3762.6976                 Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |   1.974683   .195328     6.88   0.000     1.626672    2.397149
------------------------------------------------------------------------------
```

Estimated hazard ratio = 1.97: *hazard of death about double for cadaveric recipients*

(living *x=0; cadaveric x=1*)

Stata Output

```
. stcox txtype

No. of subjects =         9750                 Number of obs    =      9750
No. of failures =          438
Time at risk    =  38236.09865
                                               LR chi2(1)       =     49.23
Log likelihood  =   -3762.6976                 Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |   1.974683   .195328     6.88   0.000     1.626672    2.397149
------------------------------------------------------------------------------
```

SE of hazard ratio

Stata Output

```
. stcox txtype

No. of subjects =         9750                 Number of obs    =      9750
No. of failures =          438
Time at risk    =  38236.09865
                                               LR chi2(1)       =     49.23
Log likelihood  =   -3762.6976                 Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |   1.974683    .195328     6.88   0.000     1.626672    2.397149
------------------------------------------------------------------------------
```

Wald test p-value < 0.05 for testing $\beta = 0$;

group hazards are statistically significantly different

Stata Output

```
. stcox txtype

No. of subjects =         9750                 Number of obs    =      9750
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Time at risk    =  38236.09865
                                               LR chi2(1)       =     49.23
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      txtype |   1.974683    .195328     6.88   0.000     1.626672    2.397149
------------------------------------------------------------------------------
```

95% CI for hazard ratio

Cox Model - Wald test and CIs

- Key: Confidence intervals and Wald tests are based on the fact that $\hat{\beta}$ has an approximate normal distribution (rule of thumb: at least 15-25 **events**)
- Test and confidence interval are based on estimators $\hat{\beta}$ for coefficients β
- Wald test: $Z = \hat{\beta} / \mathrm{SE}(\hat{\beta})$ (i.e. assume approx. normal)
- 95% CI for log HR is $(\hat{\beta} - 1.96 \times \mathrm{SE}(\hat{\beta}),\ \hat{\beta} + 1.96 \times \mathrm{SE}(\hat{\beta}))$
- 95% CI for HR is

  Upper limit: $\exp(\hat{\beta} + 1.96 \times \mathrm{SE}(\hat{\beta}))$

  Lower limit: $\exp(\hat{\beta} - 1.96 \times \mathrm{SE}(\hat{\beta}))$

Stata Output

```
. stcox txtype

No. of subjects =         9750                 Number of obs    =      9750
No. of failures =          438
Time at risk    =  38236.09865
                                               LR chi2(1)       =     49.23
Log likelihood  =   -3762.6976                 Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |   1.974683    .195328     6.88   0.000     1.626672    2.397149
------------------------------------------------------------------------------
```

Upper limit: $\exp(\hat{\beta}+1.96 \times SE(\hat{\beta}))$

Lower limit: $\exp(\hat{\beta}-1.96 \times SE(\hat{\beta}))$

Wald test $Z = \hat{\beta} / SE(\hat{\beta})$

Based on normal approx. for $\hat{\beta}$

-- Note: not HR/SE(HR)

Interpretation

"The hazard ratio of mortality for the recipient of a cadaveric kidney is about 1.97 relative to a living organ ($p < 0.001$).
The 95% CI for the hazard ratio is 1.63 to 2.40"

Lung Cancer Data

- *40* subjects with lung cancer
- Each subject underwent a Positron Emission Tomography (PET) scan
- Determined uptake of Fludeoxyglucose, (18F FDG) in standard units: (variable `fdg25`, if tumor Standard Uptake Value (SUV) > 2.5, Y/N)
- 12 subjects died during follow-up

Univariate Cox regression

```
  load lung.dta
  stset time, failure(event)

. stcox fdg25

No. of subjects =           40                     Number of obs   =        40
No. of failures =           12
Time at risk    =  1258.299998
                                                   LR chi2(1)      =     10.03
Log likelihood  =   -31.394758                     Prob > chi2     =    0.0015
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       fdg25 |    11.7675   12.35468     2.35   0.019     1.503172     92.1212
------------------------------------------------------------------------------
```

Multiple predictors

```
stcox fdg25 tumorsize multifocal
```

```
No. of subjects =           40                     Number of obs   =        40
No. of failures =           12
Time at risk    =  1258.299998
                                                   LR chi2(3)      =     13.85
Log likelihood  =    -29.48613                     Prob > chi2     =    0.0031
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       fdg25 |     7.4968   8.149509     1.85   0.064     .8903576    63.12297
   tumorsize |   1.249128   .1436471     1.93   0.053     .9970583    1.564924
  multifocal |    .296144   .3337985    -1.08   0.280     .0325141    2.697331
------------------------------------------------------------------------------
```

two or more foci of cancer

Likelihood Ratio vs. Wald

```
stcox fdg25 tumorsize multifocal
```

few failures

```
No. of subjects =           40                  Number of obs    =        40
No. of failures =           12
Time at risk    =  1258.299998

                                                LR chi2(3)       =     13.85
Log likelihood  =    -29.48613                  Prob > chi2      =    0.0031
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       fdg25 |    7.4968   8.149509     1.85   0.064     .8903576    63.12297
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  multifocal |   .296144   .3337985    -1.08   0.280     .0325141    2.697331
------------------------------------------------------------------------------
```

fairly large HR

"non"-significant Wald test

Likelihood Ratio (LR) Tests

- Tests for effect of predictor(s) by comparing log-likelihood between two models
- Fit models with and without predictor(s) of interest
- -2 times difference in log-likelihoods *is compared to a chi-square distribution*
- Important to use when number of failures is small and the HR is far from 1 (strong effect)

Performing corresponding Likelihood Ratio test for `fdg25`

- `stcox fdg25 tumorsize multifocal`
  `est store A`

  fitted the model with all predictors (the reference model), and then

  asks Stata to save log-likelihood for above model, call it "A"

- `stcox tumorsize multifocal`
  `est store B`

  fits model leaving out `fdg25`

- `lrtest A B` (or `lrtest A`)
  compare log-likelihoods *(defaults to comparing with current model)*

significant LR test

```
Likelihood-ratio test                 LR chi2(1) =       5.09
(Assumption: B nested in A)           Prb > chi2 =     0.0240
```

Likelihood Ratio vs. Wald

- Two tests for the same null hypothesis
- Typically very close in results
- Will disagree when sample size small and HR are far from 1 or/and if colinearity is present (strong correlations between predictors)
- When they disagree, the likelihood ratio test is more reliable.
- LR test always better -- just less convenient to compute

Binary Predictors

Suggest 0/1 coding:

- One-point change is easy to interpret
- Makes the baseline hazard a meaningful group
- Simplifies `lincom` when we consider interactions
  (*we will model interactions soon…)*

- Get same answer if coded 10/11

- Get same p-value but different HR if coded 0/2

Binary Predictors

```
.stcox over3cm

No. of subjects =           40                     Number of obs    =        40
No. of failures =           12
Time at risk    =  1258.299998
                                                   LR chi2(1)       =      1.26
Log likelihood  =    -35.78203                     Prob > chi2      =    0.2623
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     over3cm |   1.950839   1.196869     1.09   0.276     .5861334    6.493017
------------------------------------------------------------------------------
```

"over3cm" coded 0/1

0 = tumor less than 3 cm

1 = tumor greater than 3 cm

relative hazard for ≥ 3cm compared to < 3 cm = 1.95

Hazard is about double!

Reversed Coding

```
. recode over3cm 0=1 1=0, gen(less3cm)
. stcox less3cm

No. of subjects =           40                     Number of obs    =        40
No. of failures =           12
Time at risk    =  1258.299998
                                                   LR chi2(1)       =      1.26
Log likelihood  =    -35.78203                     Prob > chi2      =    0.2623
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     less3cm |   .5125998   .3144878    -1.09   0.276     .1540116    1.706096
------------------------------------------------------------------------------
```

"less3cm" coded 0/*1*

0 = tumor greater than 3 cm

1 = tumor less than 3 cm

LR, Wald tests same. HR and it's CI are reciprocals

.5125998=1/1.950839

Potential Pitfall: Zero Hazard Ratio

Define `fdg0` based on SUV>0

	Alive	Dead
Tumor SUV=0	4	0
Tumor SUV> 0	24	12

No Deaths in Those with Tumor SUV=0

LR test looks OK

```
stcox fdg0

No. of subjects =           40                  Number of obs    =        40
No. of failures =           12
Time at risk    =  1258.299998

                                                LR chi2(1)       =      3.48
Log likelihood  =   -34.670661                  Prob > chi2      =    0.0621
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        fdg0 |   6.53e-17   5.87e-09    -0.00   1.000            0           .
------------------------------------------------------------------------------
```

Hazard Ratio equals zero

Wald test and CI's have broken down

Reverse the Reference?

fdg_gt0: 1= SUV > 0, 0 if SUV=0

```
stcox fdg0_gt0

No. of subjects =           40                  Number of obs    =        40
No. of failures =           12
Time at risk    =  1258.299998

                                                LR chi2(1)       =      3.48
Log likelihood  =   -34.670661                  Prob > chi2      =    0.0621
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     fdg_gt0 |   2.07e+15   6.95e+22     0.00   1.000            0           .
------------------------------------------------------------------------------
```

LR test is the same

Hazard Ratio equals ∞

Wald test and CI's still don't work

Interpretation

"Zero of four subjects with a SUV of 0 died while 12/36 subjects with SUV > 0 died (estimated hazard ratio = 0); the effect did not reach statistical significance (p=0.06)"

Zero/Infinite HR

- Two sides of the same coin
  (depends on reference)
- Category has either 0% or 100% events
  (often happens with lots of categories)
- Use likelihood ratio tests: they're fine
  (Wald test performs poorly)
- Confidence intervals: see statistician
  (to calculate likelihood ratio based CI)
- Sometimes can consolidate categories to handle the issue

Categorical Predictors

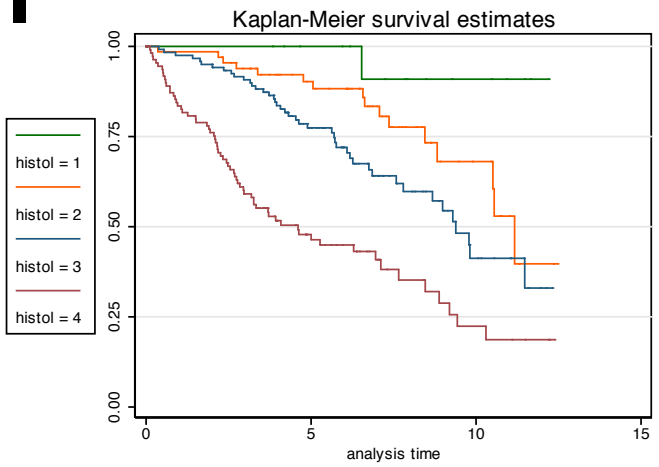
- Fit in Stata: `stcox i.categoricalpredictor`
- Many different possible tests and comparisons
  - Overall versus trend tests (unordered vs. ordered)
  - Making pairwise comparisons
- Can also use the "`i.`" syntax when binary predictor is not coded as 0/1

PBC Data

- 312 patients: Primary Biliary Cirrhosis (PBC)
- Randomized trial: DPCA vs. Placebo
- 125 subjects died
- 15 predictors: age, gender, bilirubin, histologic stage, etc.

Cox Model

Is histology a significant predictor?




```
use pbc.dta
stset years, failure(status)

. stcox sex i.histol

No. of subjects =          312
No. of failures =          125
Time at risk    =  1713.853528

                                        LR chi2(4)      =      56.72
Log likelihood  =   -611.61794          Prob > chi2     =     0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   .6072455   .1433789    -2.11   0.035     .3822823    .9645939
      histol |
           2 |   5.488862   5.667663     1.65   0.099     .7253584    41.53478
           3 |   9.459565   9.589963     2.22   0.027     1.296988    68.99321
           4 |   23.05048   23.28112     3.11   0.002     3.183916    166.8778
------------------------------------------------------------------------------

. lincom 3.histol-2.histol, hr
. lincom 4.histol-3.histol, hr
------------------------------------------------------------------------------
      3 vs 2 |   1.723411   .5056402     1.86   0.064     .9697295     3.06286
      4 vs 3 |   2.436738   .4825026     4.50   0.000     1.652955    3.592168
------------------------------------------------------------------------------
```

Overall vs. Trend Tests for Multiple Categories

- Both have same null hypothesis:
  (no difference in event risks between the groups)
- But different alternative hypothesis:
  overall: *at least one group is different*
  trend: *there is a trend across the groups*
- Use trend tests only for *ordered* predictors
  (no trend test for ethnicity)
- When trends exist, a trend test is (typically) more powerful
- For ordinal predictors it is (typically) more interpretable

Trend vs. Overall Tests

- Trend Test (Wald test)

```
contrast p.histol
Contrasts of marginal linear predictions
Margins      : asbalanced
------------------------------------------------
             |         df        chi2     P>chi2
-------------+----------------------------------
      histol |
   (linear)  |          1       10.69     0.0011
```

p = 0.001, there is a survival trend with pathology grade

- Overall Test (Wald test or LR test)

```
. testparm i.histol
 ( 1)  _Ihistol_2 = 0
 ( 2)  _Ihistol_3 = 0
 ( 3)  _Ihistol_4 = 0
chi2(  3) =   42.83
Prob > chi2 =    0.0000
```

```
. est store A
. stcox sex
. est store B
. lrtest A B
 chi2(  3) =     52.95
 Prob > chi2 =    0.0000
```

p<0.0001, at least one group different

contrast

based on assigned group values

based on order of group values

```
contrast p.histol    (or contrast q.histol)
```

```
contrast p.histol

Contrasts of marginal linear predictions
Margins      : asbalanced
------------------------------------------------
             |         df        chi2     P>chi2
-------------+----------------------------------
      histol |
   (linear)  |          1       10.69     0.0011
(quadratic)  |          1        0.60     0.4400
    (cubic)  |          1        1.26     0.2608
      Joint  |          3       42.83     0.0000
------------------------------------------------
------------------------------------------------------------
             |   Contrast   Std. Err.     [95% Conf. Interval]
-------------+----------------------------------------------
      histol |
   (linear)  |   1.113267   .3404304      .4460361    1.780499
(quadratic)  |  -.2030152   .2629276     -.7183439    .3123136
    (cubic)  |   .1682384   .1496035     -.1249791    .4614559
------------------------------------------------------------
```

Note: fitting histol as categorical followed by contrast is better than adding histol as a continuous predictor, because initial fit not constrained to be linear

Continuous Predictors *PBC data: age (in days) as predictor – what's going on?*

```
.stcox age_days

No. of subjects =          312                     Number of obs    =       312
No. of failures =          125
Time at risk    =  1713.853528
                                                   LR chi2(1)       =     20.51
Log likelihood  =   -629.72592                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    age_days |   1.00011   .0000241     4.54   0.000     1.000062    1.000157
------------------------------------------------------------------------------
```

HR is nearly one

Wald and LR tests highly significant

** Pitfall – Poor Scaling of Continuous Predictors - *PBC data: age (in days) as predictor*

```
.stcox age_days

No. of subjects =          312                     Number of obs    =       312
No. of failures =          125
Time at risk    =  1713.853528
                                                   LR chi2(1)       =     20.51
Log likelihood  =   -629.72592                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    age_days |   1.00011   .0000241     4.54   0.000     1.000062    1.000157
------------------------------------------------------------------------------
```

HR is nearly one

Wald and LR tests highly significant

PBC data: age (decades) as predictor

```
.stcox age_decades

No. of subjects =          312                     Number of obs    =       312
No. of failures =          125
Time at risk    =  1713.853528
                                                   LR chi2(1)       =     20.51
Log likelihood  =   -629.72592                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 age_decades |   1.491811   .1314533     4.54   0.000     1.255188    1.773041
------------------------------------------------------------------------------
```

HR is greater!

Wald and LR tests exactly the same

(HR per year is about 1.04)

Continuous Predictor Scaling

- HR greatly affected by the scale of measurement (e.g., age in decades, years or days)
- Choose interpretable unit change in predictor
- Statistical significance is unaffected because SE is proportional to coefficient
- Can rescale by

  (1) defining new variable

  (2) using `lincom`

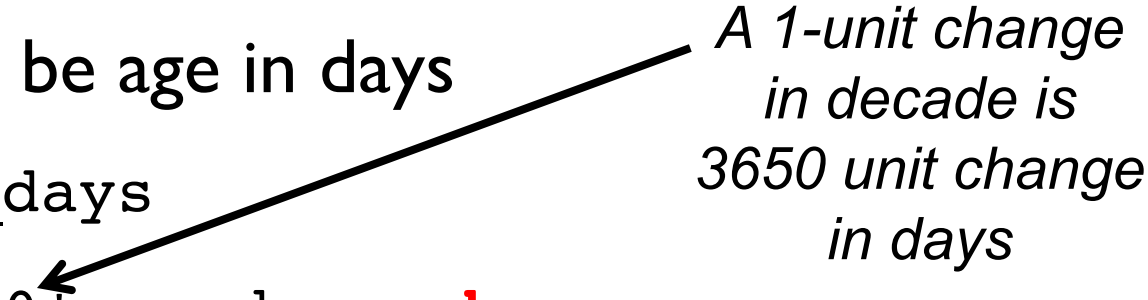
(1) Define new variable

About 3650 days per decade

- Let `age_days` be age in days
  - `gen age_decades=age_days/(3650)`
  - `stcox age_decades` *gives HR for one-decade older*
- Works for every regression -- always
- Dividing by -3650: effect of one decade younger
- The most simple method

(2) Lincom

- Let `age_days` be age in days
  - `stcox age_days`
  - `lincom 3650*age_days, hr`



gives the effect of a decade (being 3650 days older)

- The HR option is important
  otherwise get coefficient not the HR
- Less effort to implement than redefining variables (especially for one-off calculations) but *easier to make mistakes*

Confounding in the Cox model

- Handled the same way as other regression models
- Confounders added into model
- Interpretation: HR of a 1-unit change holding all other predictors constant

UNOS Kidney Example

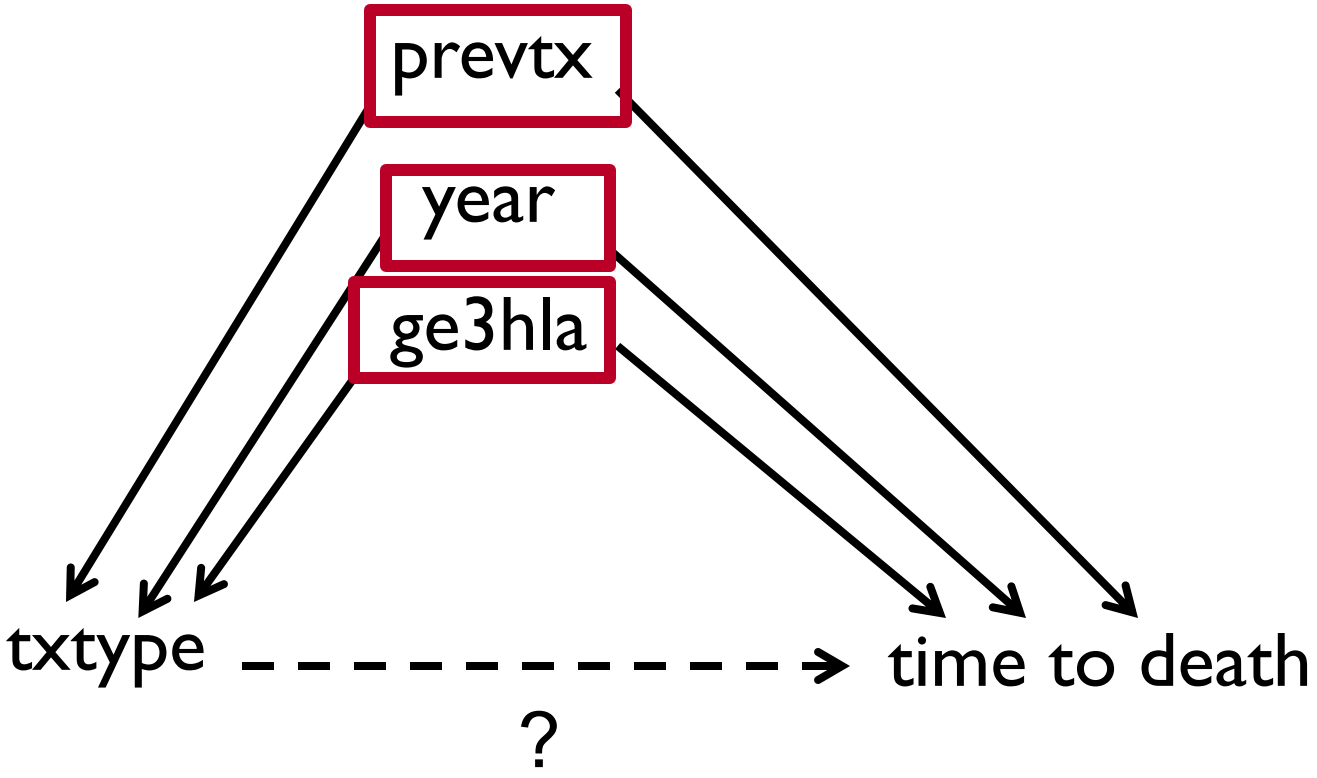
- Interest: How recipients from cadaveric donors do compared to living kidney recipients
- Unadjusted HR = 1.97, 95% CI (1.63, 2.40) – i.e., when not correcting for other predictors
- What might vary between living/cadaveric recipients?

UNOS Kidney Example

- Interest: How recipients from cadaveric donors do compared to living kidney recipients
- Unadjusted HR = 1.97, 95% CI (1.63, 2.40) – i.e., when not correcting for other predictors
- What might vary between living/cadaveric recipients? previous transplant, year of transplant, HLA match (0-2 loci vs. 3+)
- Not accounting for these differences could lead to inflated unadjusted HR

Directed Acyclic Graph (DAG)

Potential confounding:



Adjusted Model

```
.stcox txtype prevtx year ge3hla

No. of subjects =         9678                     Number of obs    =      9678
No. of failures =          407
Time at risk    =  38123.04385
                                                   LR chi2(4)       =     53.33
Log likelihood  =    -3480.778                     Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |   1.412006   .1868553     2.61   0.009     1.089417    1.830117
      prevtx |   1.316812   .1675536     2.16   0.031     1.026161    1.689788
        year |   .9456171   .0159334    -3.32   0.001     .9148981    .9773674
      ge3hla |   .7563095    .096678    -2.18   0.029     .5886967    .9716447
------------------------------------------------------------------------------
```

Attenuated HR for transplant type

vs

Unadjusted HR = 1.97

Interpretation

"The hazard ratio of mortality for the recipient of a cadaveric kidney is 1.41 compared to living kidney (p=0.01), adjusting for year of transplant, history of previous transplants and degree of HLA compatibility. The 95% CI for the hazard ratio is 1.09 to 1.83"

Is there confounding?

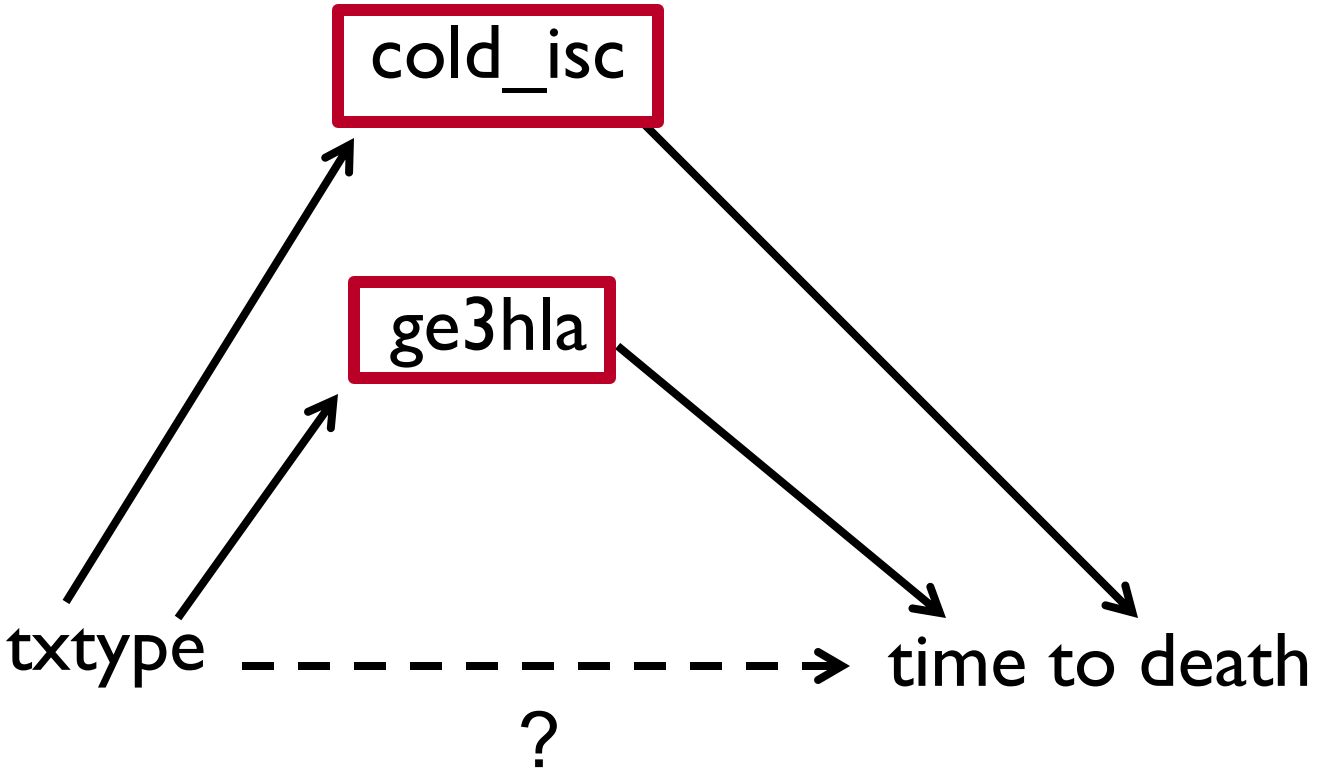
- Compare unadjusted and adjusted HR
- Screening of confounders based on association with mortality & `txtype` is too insensitive
  (if very predictive of mortality, but only slightly different between `txtype` *then can still be important confounder)*

- Examination of the associations is a way of understanding potential confounding, not a screening method for confounding
- Diff of 2.0 v. 1.4 -- clinically important?
  yes, the `txtype` *association is confounded*

Mediation

- How much of the effect of better prognosis of living recipients is explained by closer HLA match (`ge3hla`) and less transport time for the donor organ (`cold_isc`)?
- A question of mediation
- To what extent do `ge3hla` and `cold_isc` mediate the `txtype`/mortality relationship?

Directed Acyclic Graph (DAG)



After Adjustment

```
.stcox txtype ge3hla cold_isc

Log likelihood  =   -2776.2116                     Prob > chi2     =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |   1.463225   .2902374     1.92   0.055     .9919079    2.158494
      ge3hla |   .8178131    .112796    -1.46   0.145     .6240983    1.071655
    cold_isc |   1.005601   .0069314     0.81   0.418     .9921068    1.019278
------------------------------------------------------------------------------
```

Reduction in `txtype` *HR due to HLA and cold ischemia time is evidence of mediation*

Mediation Measure

$$\% \text{ mediation} = \frac{\beta_{unadj} - \beta_{adj}}{\beta_{unadj}} 100\%$$

$\beta_{unadj} = \log(1.97) = 0.678$

$\beta_{adj} = \log(1.46) = 0.378$

$$\frac{(0.678-0.378)}{0.678} \times 100 = 44\%$$

"Approximately 44% of the mortality difference between living and cadaveric kidney recipients is explained by difference in HLA match and cold ischemia time"

See Sect 4.5 of VGSM for details

Interaction

- Addressed the same way across all regression methods
  - Create product terms (use # or ## `Stata 11 on`)
  - Test of product terms reveals interaction
  - Understand interaction through series of `lincom` commands
- Predictors of graft failure in UNOS
- Is there an interaction between previous transplant and year of transplant?

Results

```
. stcox prevtx year

Log likelihood  =   -20496.194                     Prob > chi2     =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      prevtx |    2.13531   .0999166    16.21   0.000     1.948188    2.340404
        year |   1.031579   .0080216     4.00   0.000     1.015976    1.047421
------------------------------------------------------------------------------
```

```
. stcox prevtx##c.year

Log likelihood  =    -3496.171                     Prob > chi2     =    0.0001
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      prevtx |
           Y |   8.39e+56   2.75e+58     4.00   0.000     1.14e+29    6.17e+84
        year |   1.047994   .0091017     5.40   0.000     1.030306    1.065986
prevtx#c.year|
           Y |   .9367223   .0153842    -3.98   0.000     .9070499    .9673652
------------------------------------------------------------------------------
```

Results

```
. stcox prevtx year

Log likelihood  =   -20496.194                     Prob > chi2     =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      prevtx |    2.13531   .0999166    16.21   0.000     1.948188    2.340404
        year |   1.031579   .0080216     4.00   0.000     1.015976    1.047421
------------------------------------------------------------------------------
```

```
. stcox prevtx##c.year
```

huge HR for `prevtx`.

```
Log likelihood  =    -3496.171                     Prob > chi2     =    0.0001
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      prevtx |
           Y |   8.39e+56   2.75e+58     4.00   0.000     1.14e+29    6.17e+84
        year |   1.047994   .0091017     5.40   0.000     1.030306    1.065986
prevtx#c.year|
           Y |   .9367223   .0153842    -3.98   0.000     .9070499    .9673652
------------------------------------------------------------------------------
```

interaction is significant

What gives?

- The issue: the HR gives the effect of `prevtx` when all other predictors are equal to zero (including `year`!)

It's huge because it's a meaningless extrapolation!

Centered Regression

Year centered at 1995

```
. gen cyear=year-1995
  stcox prevtx##c.cyear

No. of subjects =         9678                 Number of obs    =      9678
No. of failures =         2501
Time at risk    =  38123.04385
                                               LR chi2(3)       =    252.04
Log likelihood  =   -20488.046                 Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      prevtx |
          Y |   1.937148   .1054406    12.15   0.000      1.74113    2.155234
      cyear |   1.047994   .0091017     5.40   0.000     1.030306    1.065986
    prevtx#|
  c.cyear |
          Y |   .9367223   .0153842    -3.98   0.000     .9070499    .9673652
------------------------------------------------------------------------------
```

Only `prevtx Y` has changed: corresponds to effect of prev transplant in 1995

HR Interpretation

```
stcox prevtx##c.cyear
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
prevtx						
Y	1.937148	.1054406	12.15	0.000	1.74113	2.155234
cyear	1.047994	.0091017	5.40	0.000	1.030306	1.065986
prevtx#						
c.cyear						
Y	.9367223	.0153842	-3.98	0.000	.9070499	.9673652

- `prevtx Y`: HR of previous transplant in year 1995
- `year`: HR for +1 year when `prevtx=0` (ref group)
- `prevtx#c.year Y`: HR more difficult to interpret: corresponds to an effect modifier – change in effect of year when had previous transplant (or change in effect of previous tx for each additional year)

Advice

- Don't fixate on the model HRs
- HRs estimates may not correspond to something meaningful (sometimes yes, sometimes no)
- Instead: look at test for product term
- Followed by a series of `lincom` statements
    1. What is the effect of `prevtx` in 1990?
    2. What is the effect of `prevtx` in 1995?
    3. What is the effect of `prevtx` in 2000?

Effect of Previous Transplant in 1990

	prevtx	year	product= prevtx#c.c year
previous transp.	1	-5	-5
no prev tx	0	-5	0
diff	1	0	-5

```
lincom prevtx  - 5 * prevtx#c.cyear, hr
```

lincom (centered)

Effect of Previous transplant in 1990

```
. lincom 1.prevtx  - 5 * 1.prevtx#c.cyear, hr
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   2.686016   .1950779    13.60   0.000     2.329637    3.096914
------------------------------------------------------------------------------
```

Effect of Previous transplant in 1995

```
. lincom 1.prevtx  + 0 * 1.prevtx#c.cyear, hr
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.937148   .1054406    12.15   0.000      1.74113    2.155234
------------------------------------------------------------------------------
```

Effect of Previous transplant in 2000

```
. lincom 1.prevtx  + 5 * 1.prevtx#c.cyear, hr
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.397066   .1661109     2.81   0.005     1.106648      1.7637
------------------------------------------------------------------------------
```

Interpretation

The effect of previous transplant on risk of graft failure varies by year of transplant ($p<0.0001$).

The relative hazards (and 95% Conf. Int.) for the previous transplant are

2.7 (2.3 - 3.1), 1.9 (1.7 - 2.2) and 1.4 (1.1 - 1.8), in the years 1990, 1995 and 2000, respectively.

Interaction

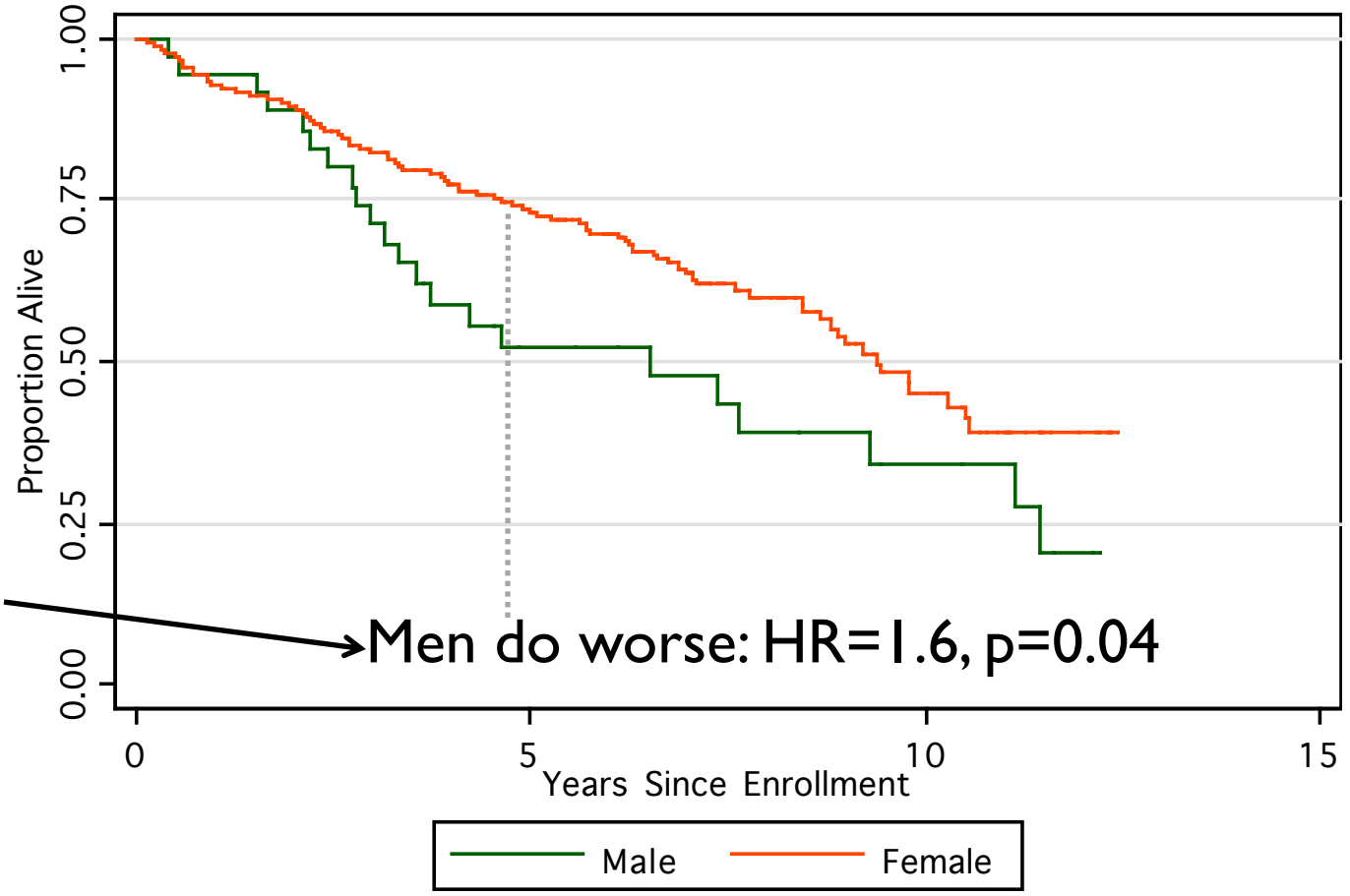
- Same advice as in linear and logistic regression models: *create product, test product, calculate lincom*
- Centering gives same test for interaction and doesn't change `lincom`
- Center makes some coefficients more interpretable, but can make use of `lincom` subject to error (if forget the variable is centered)
- Don't forget "`hr`" in those `lincom` commands

Adjusted Survival Curves

Effect of Sex: PBC data

(unadjusted comparison)

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



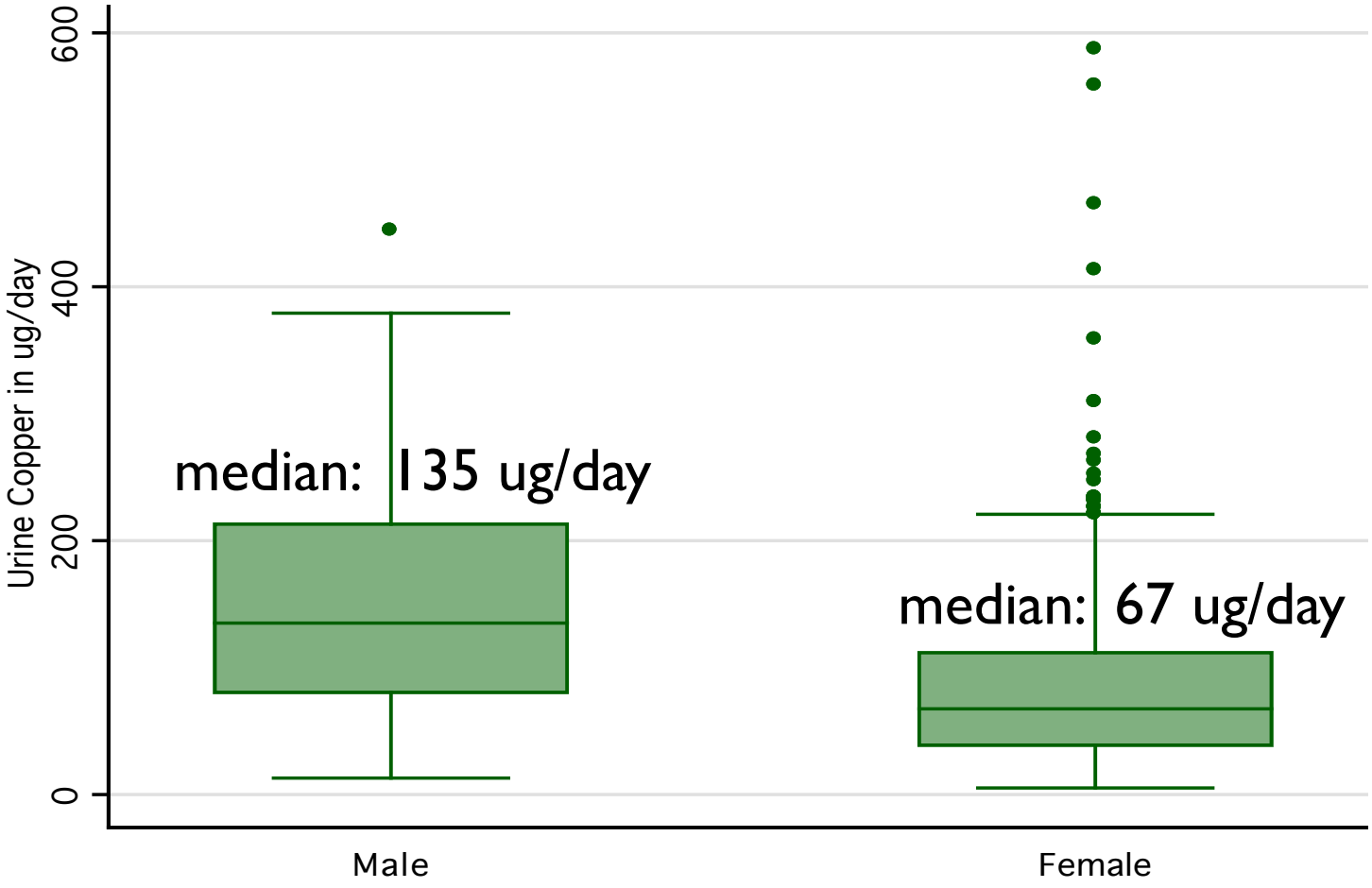

```
stcox sex
```

(Cox model fit)

→ Men do worse: HR=1.6, p=0.04

Men: Higher Copper

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



Adjusted Survival Curves (for Cox model)

- Would like to visualize the adjusted effects of variables (e.g., controlling for copper)
- Can make adjusted survival prediction based on a Cox model

Under the Cox Model

Consider S(t|x): survival function (event-free proportion at time t) for someone with predictors x

$S_0(t)$:= baseline survival function

= survival function when all predictors equal zero

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

(β's are the coefficients from the Cox model)

- In Cox model we see estimates of $\exp(\beta_p)$
- In background, Stata calculates estimates of $S_0(t)$

Adjusted Curves 1

- Look at effect of x_1 (sex) adjusting for x_2 (copper)
- Create two curves with same value for x_2 *(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 start with overall mean…

Adjusted Curves 2

```
. 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 copper=97.6) at2(sex=1 copper=97.6)
```

stcurve: gives predicted curves

survival: graph survival (not hazard default)

at1: (predictor values for curve 1)

at2: (predictor values for curve 2)

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

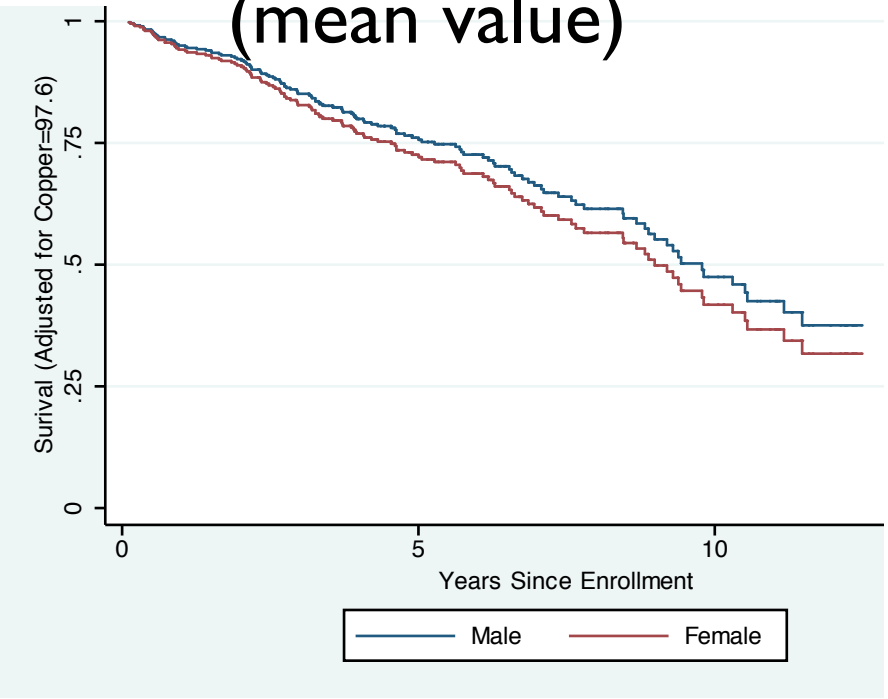
```
. stcurve, survival at1(sex=0) at2(sex=1)
```

gives same result

Adjusted Curves 3

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

copper set to 97.6
(mean value)

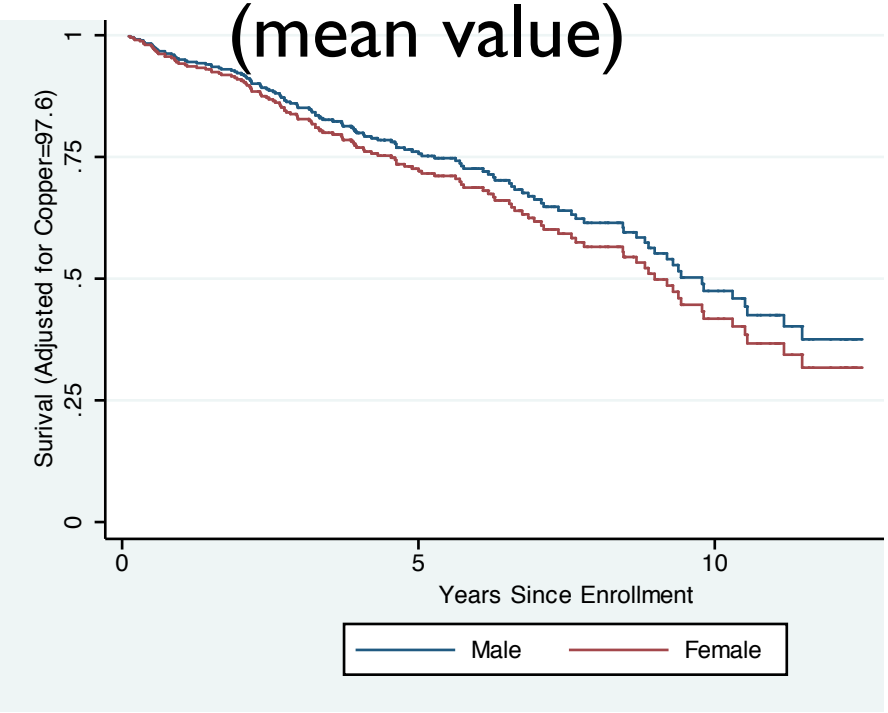


Adjusted Curves 4

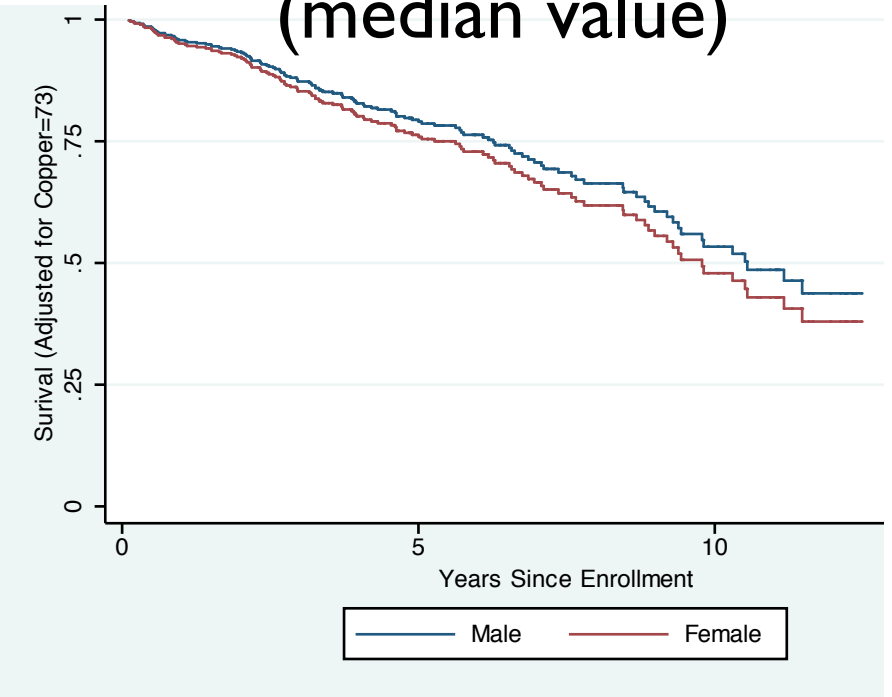
Let's compare mean vs. median copper as reference

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



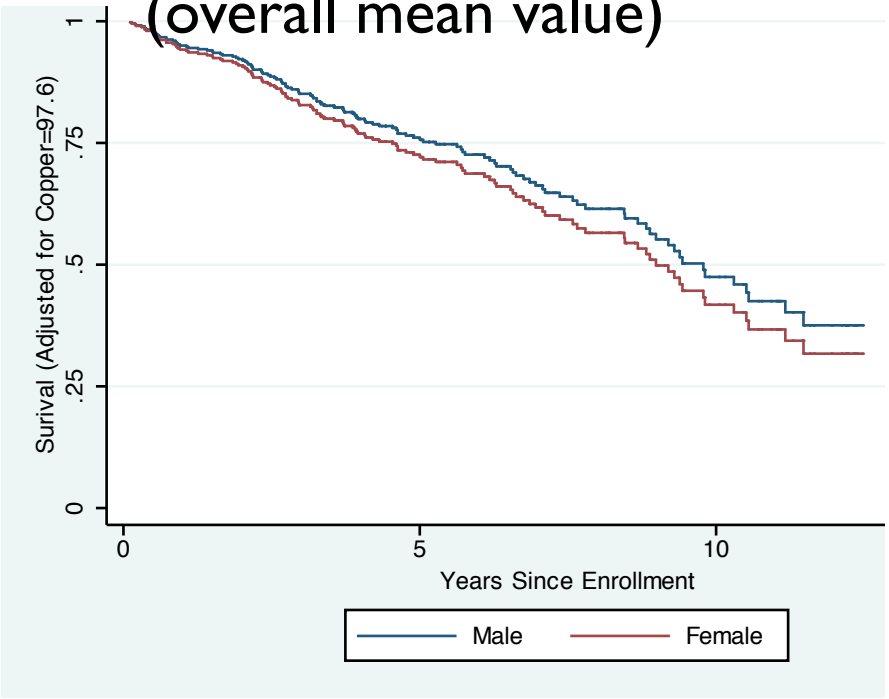
reference value for copper matters

Adjusted Curves 5

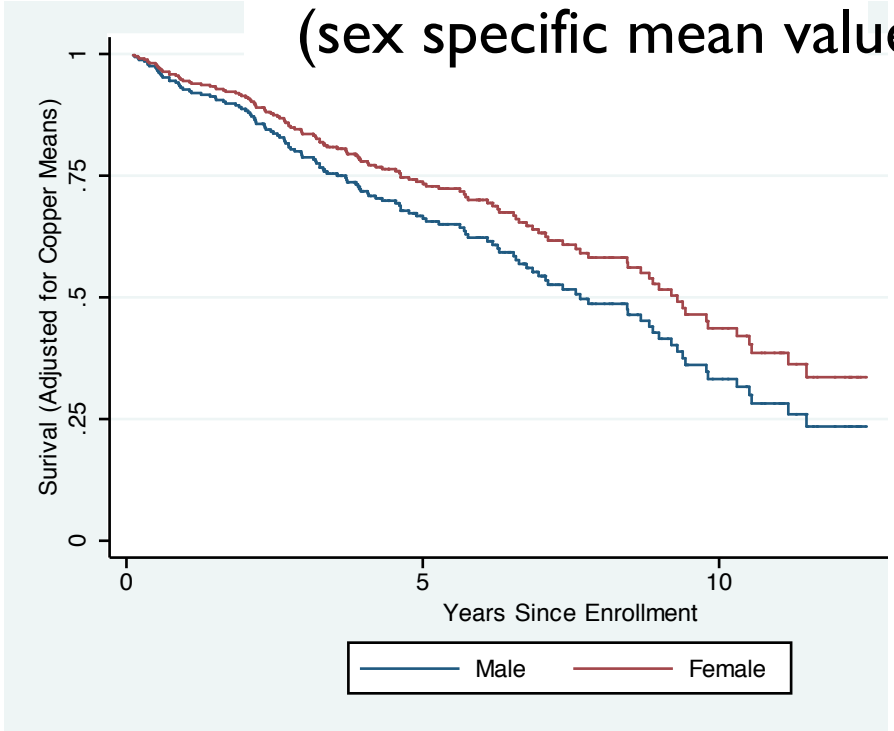
Now compare overall vs. group specific copper means as reference

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

- 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
- In Stata, `stcurve` is a flexible tool for creating adjusted survival curves
- Summary: Look at survival curves with `stcurve` while fixing other variables in the model

Next Lecture
(extensions to the Cox model)

- Reading VGSM, Ch. 6.3 - 6.5
- Time-dependent covariates
- Diagnostics (model checking) - proportional hazards?
- Non-proportional Hazards: Stratification
- Non-proportional Hazards: generate time-dependent covariates trick
- Followed by homework session

Don't forget…

- Project description and date limitations due today
- HW 1 due by start of lecture 4/17/18
- Lab 2 (available on syllabus page) session on Thursday MH 1400
- Reading for next lecture VGSM 6.3 - 6.5