Biostatistics 209, Lab #2 Discussion

3. Unadjusted and Adjusted Effect

`load` *directory_location*`/pbc.dat`

```
stset years, failure(status)
```

- Examine the effect of `sex` (**1=female, 0=male**) on survival both graphically and in a Cox model

```
sts graph, by(sex)
stcox sex

No. of subjects =          312                     Number of obs    =       312
No. of failures =          125
Time at risk    =  1713.853528
                                                   LR chi2(1)       =      3.77
Log likelihood  =   -638.09345                     Prob > chi2      =    0.0521

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   .6163198    .145757    -2.05   0.041     .3877043    .9797418
------------------------------------------------------------------------------
```

Women are at lower risk of death (38% reduction) compared to men. Alternatively, you could state that the hazard ratio of death for men is 1.62=1/.616 (a 62% increase).

- Fit a model adjusting for the effect of sex on the following possible confounding variables: `age`, log bilirubin (`logbili`) and triglycerides (`trigli`)

```
stcox sex age logbili trigli

No. of subjects =          282                     Number of obs    =       282
No. of failures =          113
Time at risk    =  1538.294321
                                                   LR chi2(4)       =    137.63
Log likelihood  =   -494.55422                     Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         sex |   1.018364   .2589741     0.07   0.943     .6186412    1.676359
         age |     1.0439    .009745     4.60   0.000     1.024974    1.063176
     logbili |   3.098469   .3423258    10.24   0.000     2.495195    3.847599
      trigli |   .9975208   .0014368    -1.72   0.085     .9947087    1.000341
------------------------------------------------------------------------------
```

Extra question: which variable(s) has missing values?

- Interpret the results.

The hazard ratio for female sex (adjusting for bilirubin, age and triglycerides) is 1.02 (p=0.943) with 95% CI (0.62 to 1.68). After adjustment, the sex difference in mortality did not reach statistical significance.

4. Statistical Interaction

Consider an interaction between `sex` and baseline level of copper in the urine (`copper`).

- Fit the interaction model
  `stcox sex##c.copper, nolog`
- Question 4.1: Does there appear to be a significant interaction?

```
No. of subjects =          310                 Number of obs    =       310
No. of failures =          124
Time at risk    =  1706.466806
                                               LR chi2(3)       =     64.60
Log likelihood  =   -601.59901                 Prob > chi2      =    0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       1.sex |   .3901488   .1581514    -2.32   0.020     .1762729     .863525
      copper |   1.001955   .0019675     0.99   0.320     .9981062    1.005819
             |
sex#c.copper |
          1  |   1.006169   .0021351     2.90   0.004     1.001993    1.010362
------------------------------------------------------------------------------
```

We see that the interaction term is highly significant, p = 0.004.

- Questions 4.2 & 4.3: Consider the use of the following tables to derive the `lincom` statements for **a 10 unit change** in urine copper for female and male subjects

	Female Subjects			***Male Subjects***		
	sex	**copper**	**interaction**	**sex**	**copper**	**interaction**
copper = x+10	1	x+10	x+10	0	x+10	0
copper = x	1	x	x	0	x	0
difference	0	10	10	0	10	0

Which leads to

For males: `lincom 10*copper, hr`

```
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.019723   .0200241     0.99   0.320     .9812226    1.059735
------------------------------------------------------------------------------
```

The effect of a 10-unit increase in copper among men is an 2% increase in the hazard of death (p=0.32), 95% confidence interval (-2% to +6%).

For females: `lincom 10*copper + 10* 1.sex#c.copper, hr`

```
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.084404   .0091777     9.57   0.000     1.066564    1.102542
------------------------------------------------------------------------------
```

The effect of a 10-unit increase in copper among women is an 8% increase in the hazard of death (p < 0.0001), 95% confidence interval (7% to 10%).

It appears that copper increases the risk of death for both sexes, but that such an effect is much more pronounced in women than in men. In men, copper is not a statistically significant predictor of mortality.

- Fill out the following tables to derive the relative hazard between the sexes at a copper of 17, 73 and 256 (the 5%, 50%, and 95%-ile of copper values)

Copper of	***17***			***73***		
	sex	**copper**	**interaction**	**sex**	**copper**	**interaction**
Female	1	17	17	1	73	73
Male	0	17	0	0	73	0
difference	1	0	17	1	0	73

Copper of	***256***		
	sex	**copper**	**interaction**
Female	1	256	256
Male	0	256	0
difference	1	0	256

Which leads to

Copper of 17

```
lincom 1.sex +  17* 1.sex#c.copper, hr

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .4331466   .1632321    -2.22   0.026     .2069465    .9065917
------------------------------------------------------------------------------
```

Copper of 73

```
lincom 1.sex +  73* 1.sex#c.copper, hr

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .6112276   .1802483    -1.67   0.095     .3429157    1.089478
------------------------------------------------------------------------------
```

Copper of 256

```
lincom 1.sex +  256* 1.sex#c.copper, hr

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.883519   .6074192     1.96   0.050     1.001071    3.543851
------------------------------------------------------------------------------
```

- Interpret the results

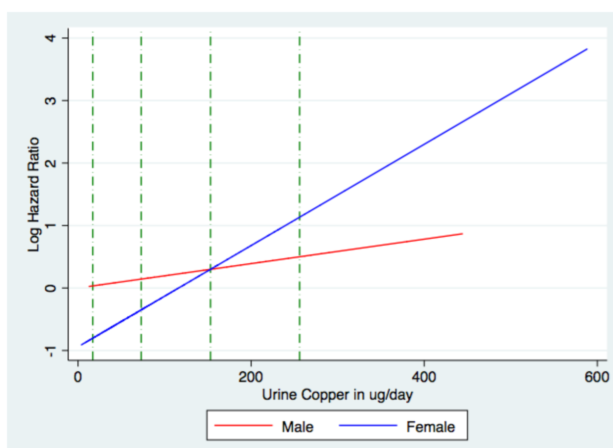
We see that at a copper of 17, 73 and 256: the hazard ratios vary from 0.43, 0.61, to 1.88. Suggesting that women are at lower risk of death with lower values of copper and at higher risk as the copper values increase.

- It can be helpful to graph the interaction. It is most easily visualized **<u>on the log hazard scale</u>** (i.e., on the scale of the β coefficients).

`predict out, xb` (*calculate the log hazard and put them in variable "out"*)

-- Now, use the Stata menus to graphs the log hazards for female and male subjects by copper.

  - Go to, "Graphics", "Twoway graph"
  - Click "Create", select "Basic Plot" and "Line" as plot type
  - Y-variable: `out`, X-variable: `copper` Click on box "Sort on x variable"
  - Click on the tab "if/in", fill in "**`sex==0`**" and click "Accept"
  - Click "Edit"
  - Click on "Line Properties", select "Red" for Line Color and click "Accept"
  - Click "Accept"
  - Click "Create" again (*repeating the above steps for another line in different color*), select "Basic Plot" and "Line" as plot type
  - Y-variable: `out`, X-variable: `copper` Click on box "Sort on x variable"
  - Click on the tab "if/in", fill in "**`sex==1`**" and click "Accept"
  - Look at the Tabs at the Top
  - Click on "Y-axis", fill in **`Log Hazard Ratio`** under Title
  - Click on "Legend", Check "Override Default Keys"
  - Fill in **`1 "Male" 2 "Female"`** under "Specify order of keys....."
  - Click on "X axis" and then click on "Reference lines"
  - Check "Add lines to graph at specified x axis values" and type "17 73 153 256" in box
  - Pattern select "Dash dot"
  - Color select "Green"
  - Click "submit"



The sequence of Stata menu commands is equivalent to:

```
twoway (line out copper if sex==0, sort lcolor(red)) (line out copper if
sex==1, sort lcolor(blue)), ytitle(Log Hazard Ratio) xline(17 73 153
256, lpattern(dash_dot) lcolor(green)) legend(order(1 "Male" 2
"Female"))
```

We see from the graph that men have a higher risk of death than women at lower levels of copper.

At a copper value of 153 the above `lincom` *equation (i.e.,* `lincom 1.sex + 153 * 1.sex#c.copper`*) would lead to β=0, i.e., HR=1. -- leading to -1 times the ratio of the coefficient for* `sex` *to the coefficient for* `interaction` *=* `-log(.3901488)/log(1.006169)=153`*), the curves cross and then men are at lower risk than women. We could call this a qualified interaction, since the comparison of which sex has a better prognosis changes places in different ranges of values for copper.*

You could save estimates of the coefficients (log hazard ratios) by

```
matrix giveAname =e(b)          (to save the values of coefficients)
matrix list giveAname           (to see the values of log hazards ratios)
```

```
            giveAname [1,5]
                     0b.          1.                    0b.sex#       1.sex#
                     sex          sex       copper    co.copper     c.copper
            y1         0   -.94122708    .00195315            0    .00614988
```

then do the calculation as

```
display -giveAname[1,2] / giveAname[1,5]
            153.04806
```

Also, notice that higher copper is a considerably more adverse marker for women compared to men.

This graph reveals the awkward estimated sex effect of HR=0.39, which represents a log hazard ratio of -0.94 for women compared to men based on <u>a copper value of zero</u> - perhaps not the best value of copper for comparison of the sexes. The reference value could be changed, e.g., by centering copper to its mean value. These graphs may not be ideal for publication in a paper, but they provide a useful tool for understanding the nature and direction of an interaction.

5. Adjusted Survival Curves

Return to the issue we considered in question 3, the effect of sex on mortality after adjusting for log bilirubin, age and triglycerides.

- Re-run (or restore) the adjusted regression
  `stcox sex age logbili trigli`
- Graph the adjusted survival curve.

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

What values of age, logbili and trigli are the curves adjusted at?

- Regraph the Kaplan-Meiers for comparison

```
sts graph, by(sex)
```

You can tweak the graphs to label them better. The commands to use are

```
stcurve, survival at1( sex=0 ) at2( sex=1 )  title("Cox Regression")
legend(order(1 "Male" 2 "Female")) ytitle("Proportion Surviving")
scheme(s1color)
```

```
sts graph, by(sex) title("Kaplan-Meier estimates") legend(order(1 "Male"
2 "Female")) ytitle("Proportion Surviving") scheme(s1color)
```