Survival Analysis II

Reading VGSM 6.2.5 - 6.2.13

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- Project description due today
- Hwk #1 due next Tuesday, 4/14 – upload via syllabus
- Reading for next lecture VGSM 6.3 - 6.5
- Lab. 2 on web site - for this Thursday Rm MH 1400
- Check and use Biostat 209 discussion forum

In this lecture

- Review Survival data and the Cox model
- Interpreting Cox model fits
- Binary, categorical and continuous predictors
- Confounding and mediation
- Review of interaction effects
- Interaction terms in the Cox model

Survival review: key concepts

- Survival data: right censoring
- Linear/logistic regression sub-optimal
- Kaplan-Meier/logrank "raw" summary/test
- Hazard function: $\longrightarrow$ "instantaneous risk"
- Proportional hazards assumption: ratio of hazards is constant over time
- Cox model - no baseline hazard model
- Effect of 1 unit change in a predictor on Survival, given in terms of "hazard ratio": the *relative hazard*

Cox regression review

- Proportional hazards model → log(hazard ratio) depends linearly on regression coefficients
- $h(t|x) = h_0(t) \exp(\beta_1 x_1 + \ldots + \beta_p x_p)$
- $\log(h(t|x)/h_0(t)) = \beta_1 x_1 + \ldots + \beta_p x_p$
- C.f. *log-odds* in logistic regression and *outcome* in linear regression - each depends linearly on regression coefficients

Review Cox Model

- Assumes Proportional Hazards
- Can summarize predictor effects based on coefficients, β, or in terms of hazard ratios, $\exp(\beta)$
- Hazard ratios work better for interpretation
- Math simpler based on coefficients (easy to go back and forth)

Cox Model - Wald test and CIs

- 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
- 95% CI for HR is

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

  Lower limit: $\exp(\hat{\beta} - 1.96 \times SE(\hat{\beta}))$
- Wald test: $Z = \hat{\beta}/SE(\hat{\beta})$ (i.e. assume approx. normal)

Lung Cancer Data

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

Wald test and CI

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

```
. stcox fdgavid

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]
-------------+----------------------------------------------------------------
     fdgavid |    11.7675   12.35468     2.35   0.019     1.503172    92.1212
------------------------------------------------------------------------------
```

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

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

Wald test: $Z = \hat{\beta}/SE(\hat{\beta})$ -- *Note: not* HR/SE(HR)

Normal approx. for coeffs.

CIs are calculated from coefficients not hazard directly

Multiple predictors

```
stcox fdgavid 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]
-------------+----------------------------------------------------------------
     fdgavid |     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
------------------------------------------------------------------------------
```

Likelihood Ratio (LR) Tests

- Tests for effect of predictor(s) by comparing log-likelihood between two models
- Fit models with and without predictor(s) to be tested
- -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)

Likelihood Ratio vs. Wald

```
stcox fdgavid 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]
-------------+----------------------------------------------------------------
     fdgavid |     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
------------------------------------------------------------------------------
```

fairly large HR

“non”-significant Wald test

Performing corresponding Likelihood Ratio test for `fdgavid`

- `stcox fdgavid 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 `fdgavid`

- `lrtest A B` (or `lrtest A`)
  compare log-likelihoods *(defaults to the previous 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

```
.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!

Binary Predictors

- Suggest 0/1 coding
- One-point change is easy to interpret
- Makes the baseline hazard an identifiable group
  e.g., *those with tumors < 3 cm*
- Simplifies lincoms 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

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 was borderline statistically significant (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

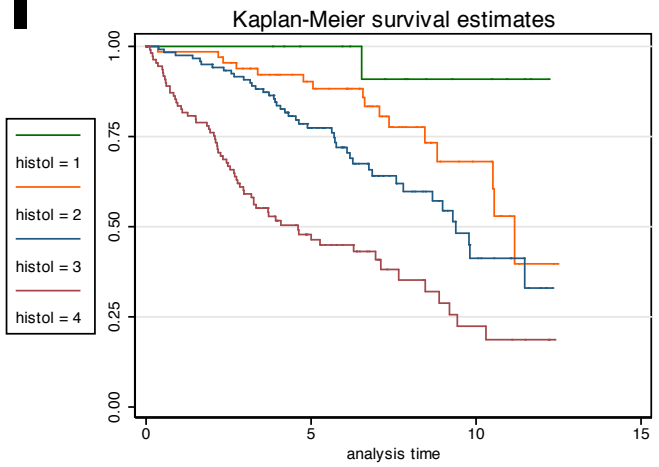
- Fit in Stata: `stcox i.categoricalpredictor`
- Many different possible tests and comparisons
  - Overall versus trend tests (unordered vs. ordered)
  - Making pairwise comparisons
- Can also use the "`i.`" syntax when binary predictor is not coded as 0/1

PBC Data

- 312 patients: Primary Biliary Cirrhosis (PBC)
- Randomized trial: DPCA vs. Placebo
- 125 subjects died
- 15 predictors: hepatomegaly, spiders, bilirubin, 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)

```
. test -1* 2.histol + 3.histol + 3* 4.histol = 0

           chi2(  1) =   10.69
         Prob > chi2 =    0.0011
```

appropriate linear combination from VGSM table 4.8, p. 87

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

test vs. contrast

Trend Test

```
use pbc.dta
stset years, failure(status)
stcox sex i.histol, nolog

test -1* 2.histol + 3.histol + 3* 4.histol = 0

           chi2(  1) =   10.69
         Prob > chi2 =    0.0011
```

appropriate linear combination from VGSM table 4.8, p. 87

Alternatively,

based on group values

based on order of group values

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

test vs. contrast

```
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
------------------------------------------------------------------
```

Same as for test

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)
- Statistical significance is unaffected because SE is proportional to coefficient
- Choose interpretable unit change in predictor
- Can rescale by

  (1) defining new variable

  (2) using `lincom`

  (3) direct calculation

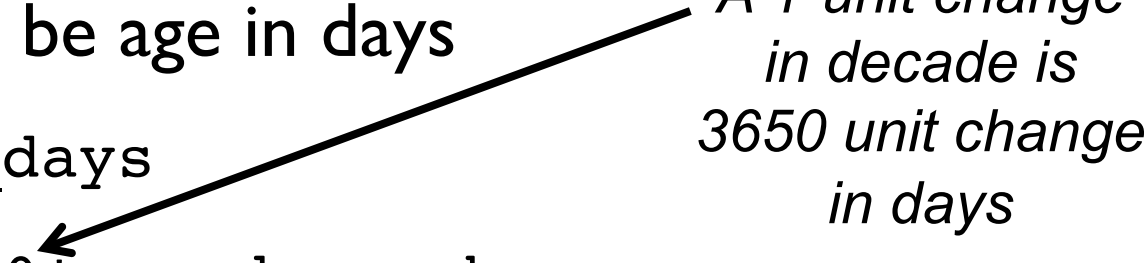
(1) Define new variable

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*

(3) Direct Calculation

- Let `HRage_d` be the HR for age in days
  - HR for decade = `(HRage_days)`^{3650}
  - HR for confidence limits: also raised to 3650
  - test, p-values exactly the same
- HR for *k*-days = `(Hrage_days)`^{k}
  k is any arbitrary number, could even be negative
- Rarely need to use this method
  but useful to know what calculations are going on

(3) Direct Calculation

	HR	Lower 95% CI	Upper 95% CI	Wald p-value	LR p-value
Day	1.00011	1.000062	1.00016	<0.0001	<0.0001
Decade	1.00011^{3650} =1.49	1.000062^{3650} = 1.26	1.00016^{3650} = 1.79	same as above	same as above

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
- All predictors adjust for each other

UNOS Kidney Example

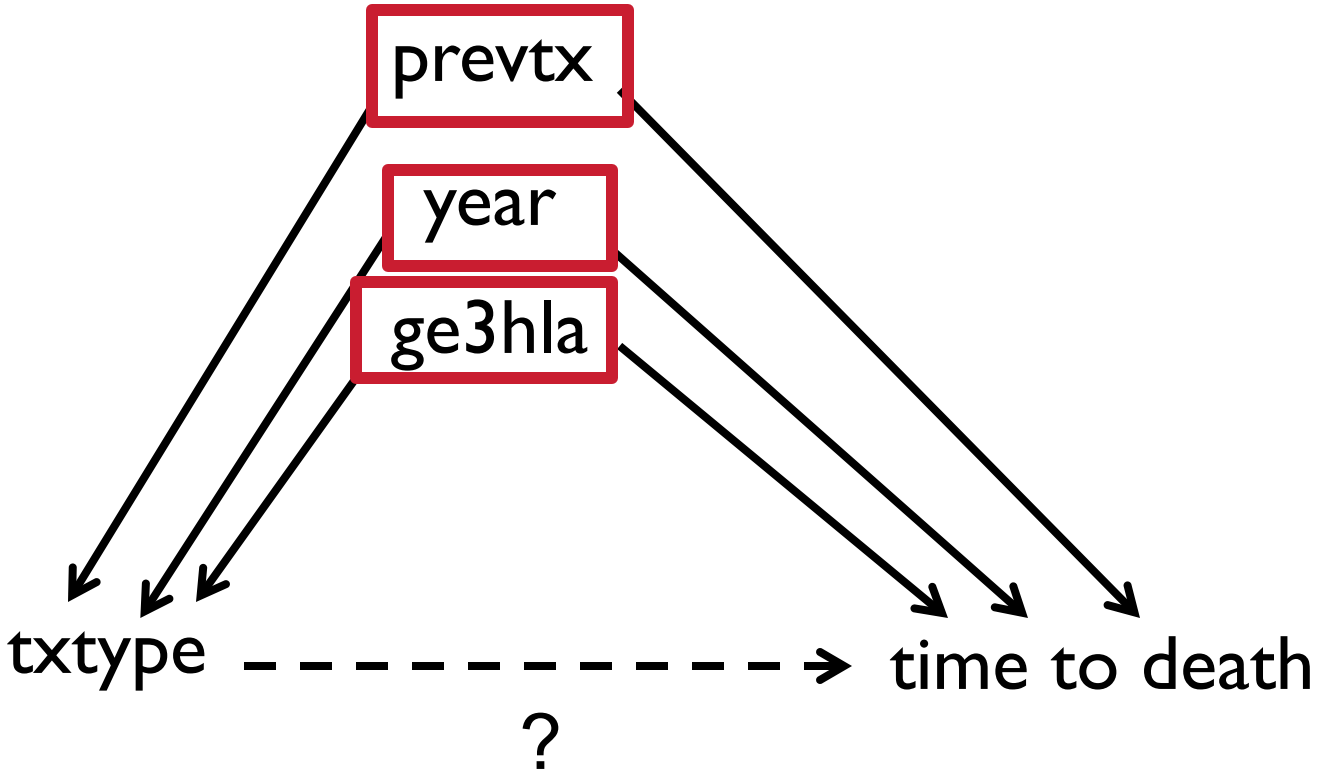
- Interest: How recipients from cadaveric donors do compared to living kidney recipients
- Unadjusted HR = 1.97, 95% CI (1.63, 2.40) – i.e., when not correcting for other predictors
- What might vary between living/cadaveric recipients?

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?

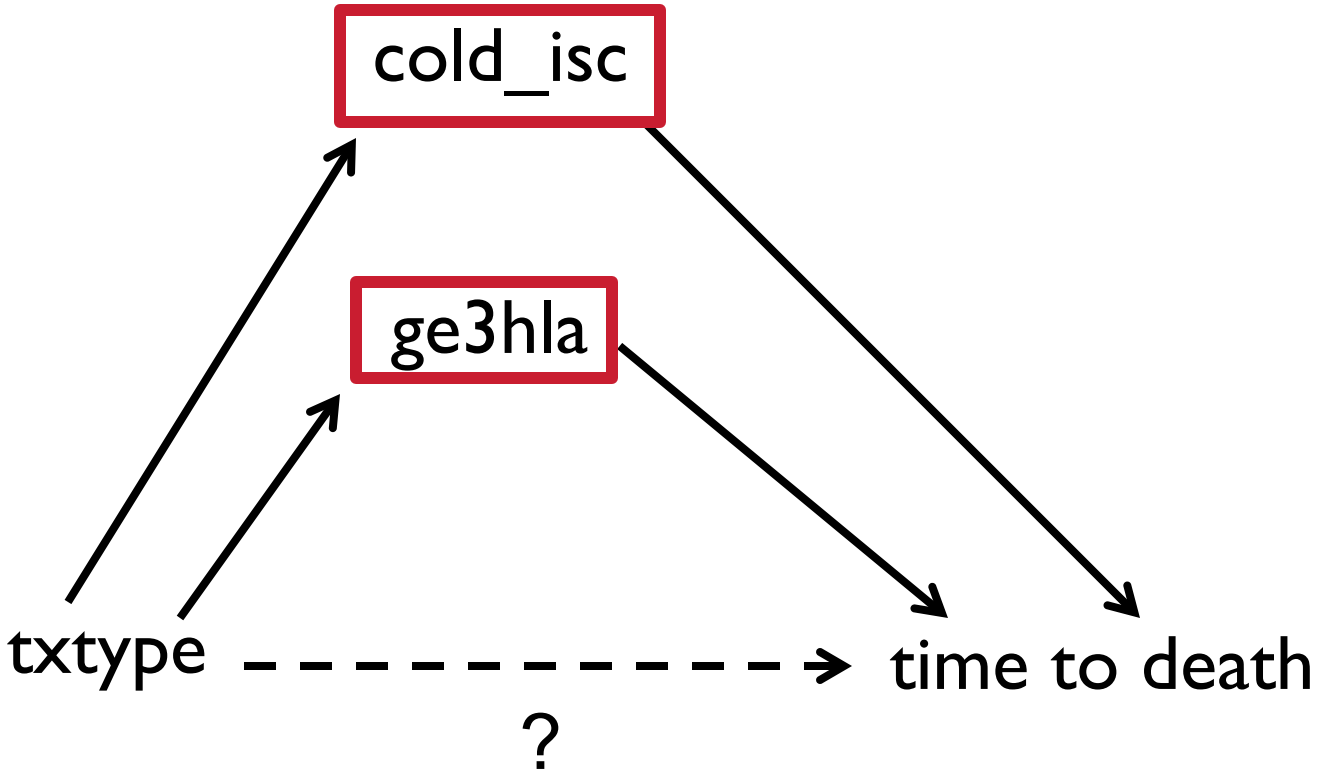
- Compare unadjusted and adjusted HR
- Screening of confounders based on association with mortality & `txtype` is too insensitive
  (if very predictive of mortality, but only slightly different between `txtype` *then can still be important confounder)*

- 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

Aside: interactions in regression

Binary Interactions

Outcome = Systolic BP

No interaction

	Drink = 0	Drink = 1
Smoke = 1	a	a + b
Smoke = 0	0	b

a = Smoking effect, b = Drinking effect

Binary Interactions

Outcome = Systolic BP

Interaction

	Drink = 0	Drink = 1	
Smoke = 1	a	a + b + c	$c \neq 0$
Smoke = 0	0	b	

a = Smoking effect, b = Drinking effect, c = interaction

Binary Interaction with a Continuous Variable

$$y = \alpha + x_{age}\beta_{age} + x_{Dx}\beta_{Dx} + x_{age}x_{diag.}\beta_{inter} + \varepsilon$$

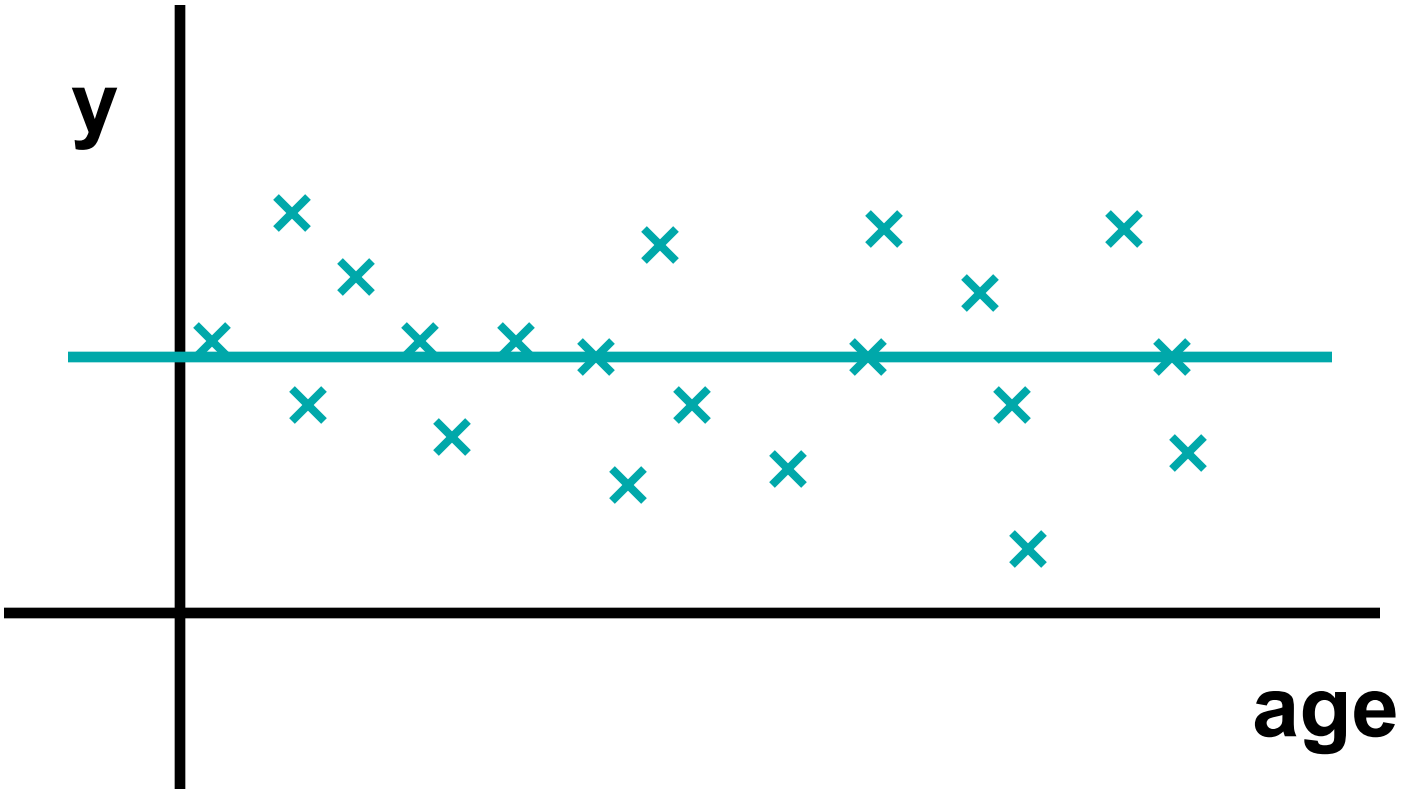
y = cognition score - outcome

$Dx = 1$, AD (Alzheimer's)

$Dx = 0$, HC (Healthy Control)

Case 1

$$\beta_{age} = 0, \beta_{Dx} = 0, \beta_{inter} = 0$$



$$y = \alpha + x_{age}\beta_{age} + x_{Dx}\beta_{Dx} + x_{age}x_{diag.}\beta_{inter} + \varepsilon$$

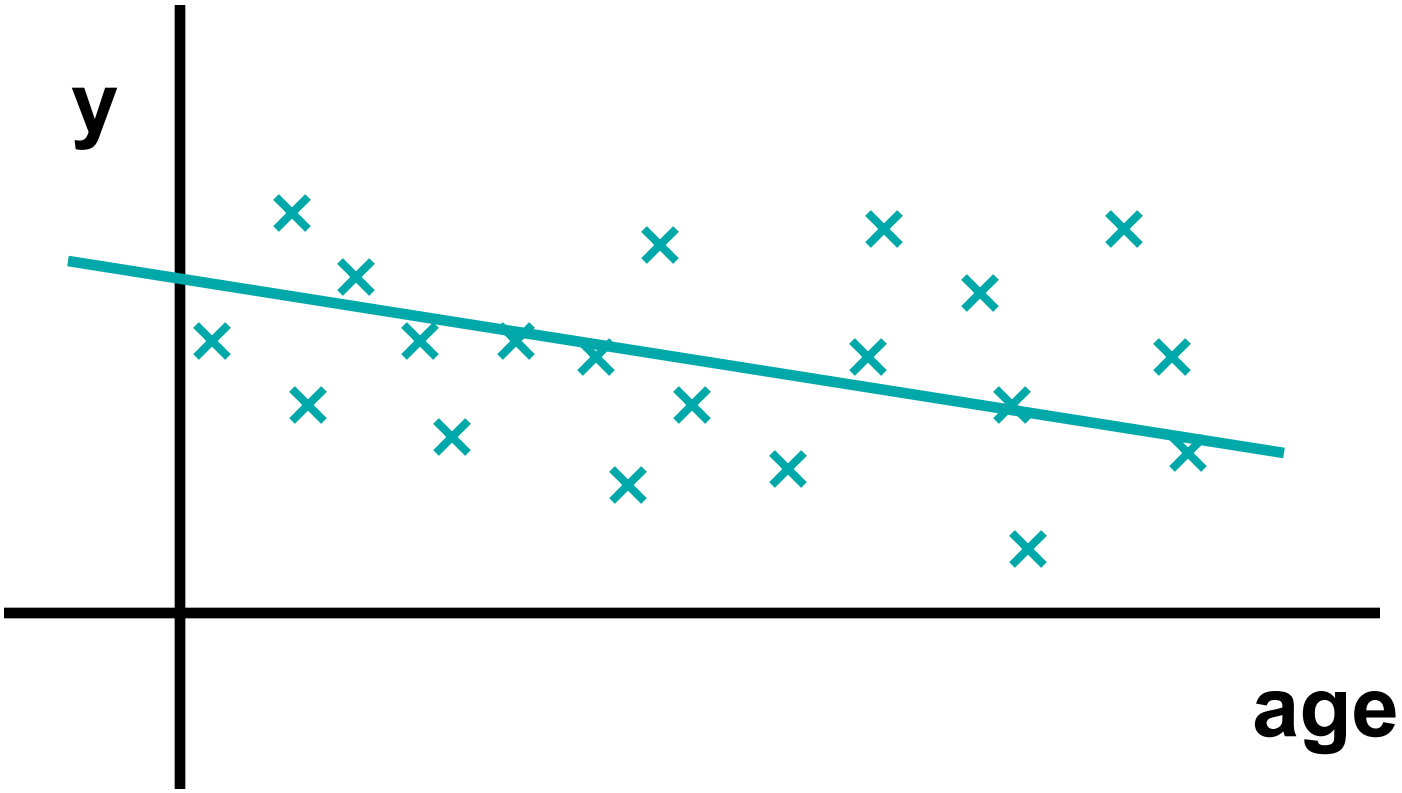
y = cognition score - outcome

$Dx = 1$, AD (Alzheimer's)

$Dx = 0$, HC (Healthy Control)

Case 2

$$\beta_{age} \neq 0, \beta_{Dx} = 0, \beta_{inter} = 0$$



$$y = \alpha + x_{age}\beta_{age} + x_{Dx}\beta_{Dx} + x_{age}x_{diag.}\beta_{inter} + \varepsilon$$

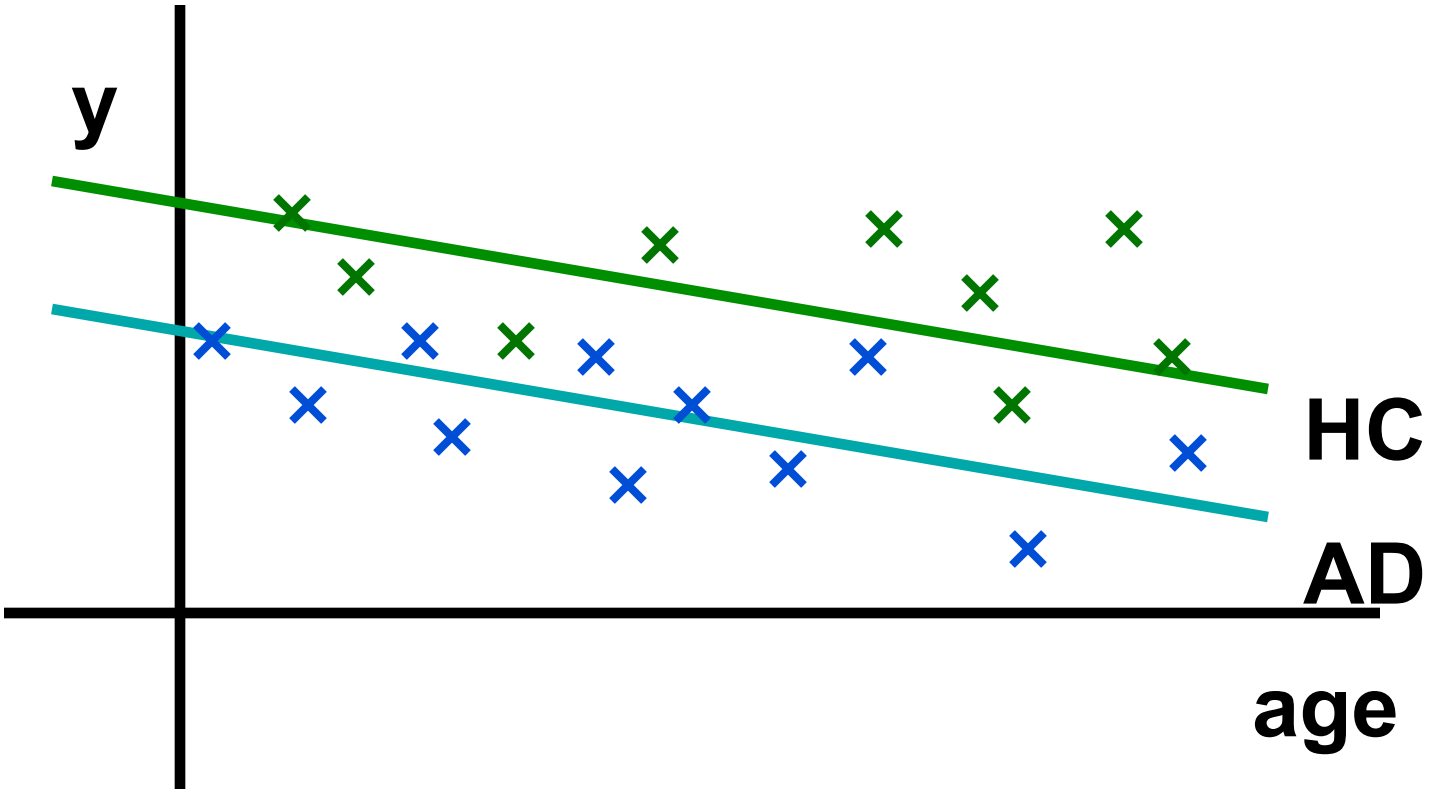
y = cognition score - outcome

$Dx = 1$, AD (Alzheimer's)

$Dx = 0$, HC (Healthy Control)

Case 3

$$\beta_{age} \neq 0, \beta_{Dx} \neq 0, \beta_{inter} = 0$$



$$y = \alpha + x_{age}\beta_{age} + x_{Dx}\beta_{Dx} + x_{age}x_{diag.}\beta_{inter} + \varepsilon$$

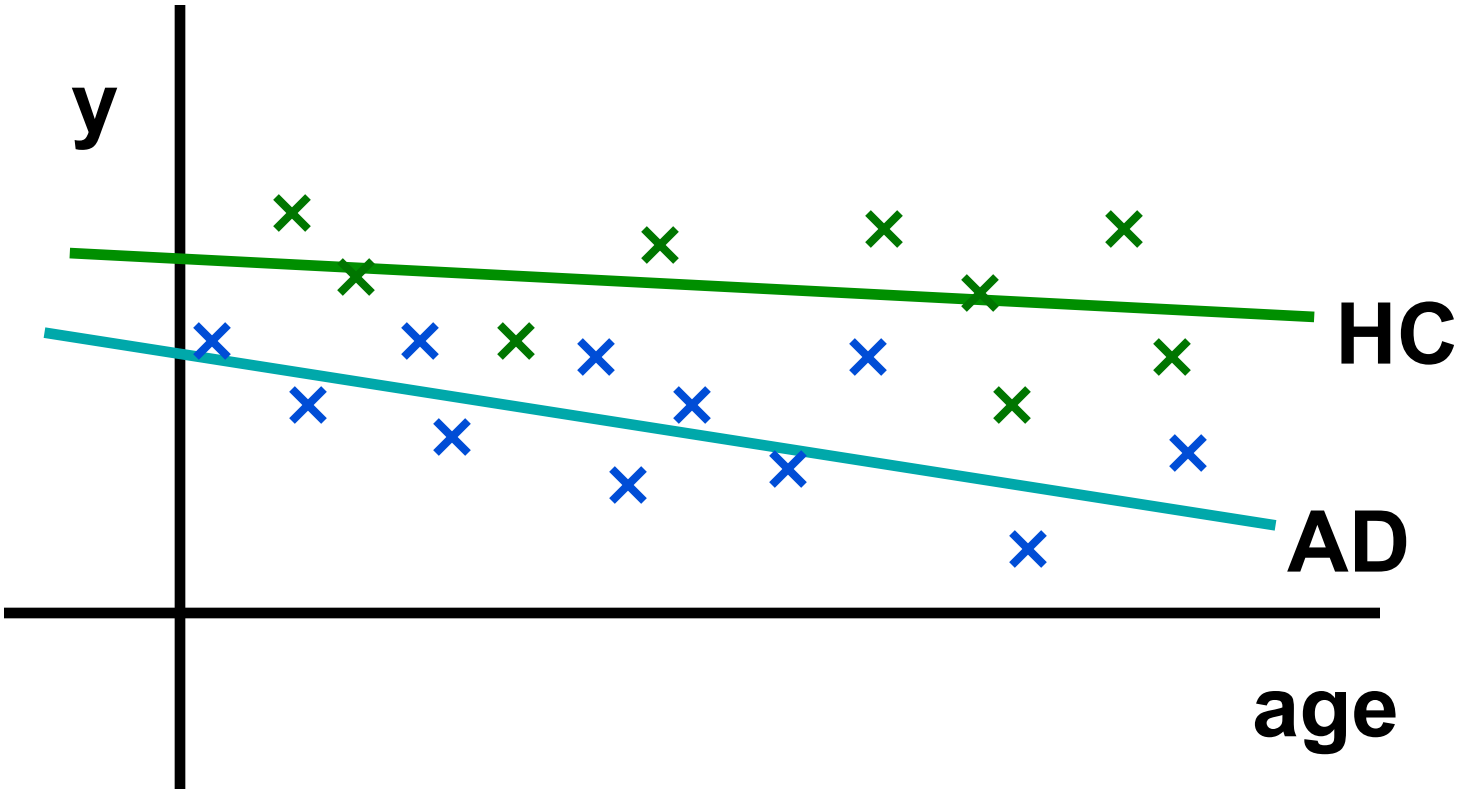
y = cognition score - outcome

$Dx = 1$, AD (Alzheimer's)

$Dx = 0$, HC (Healthy Control)

Case 4

$$\beta_{age} \neq 0, \beta_{Dx} \neq 0, \beta_{inter} \neq 0$$



$$y = \alpha + x_{age}\beta_{age} + x_{Dx}\beta_{Dx} + x_{age}x_{diag.}\beta_{inter} + \varepsilon$$

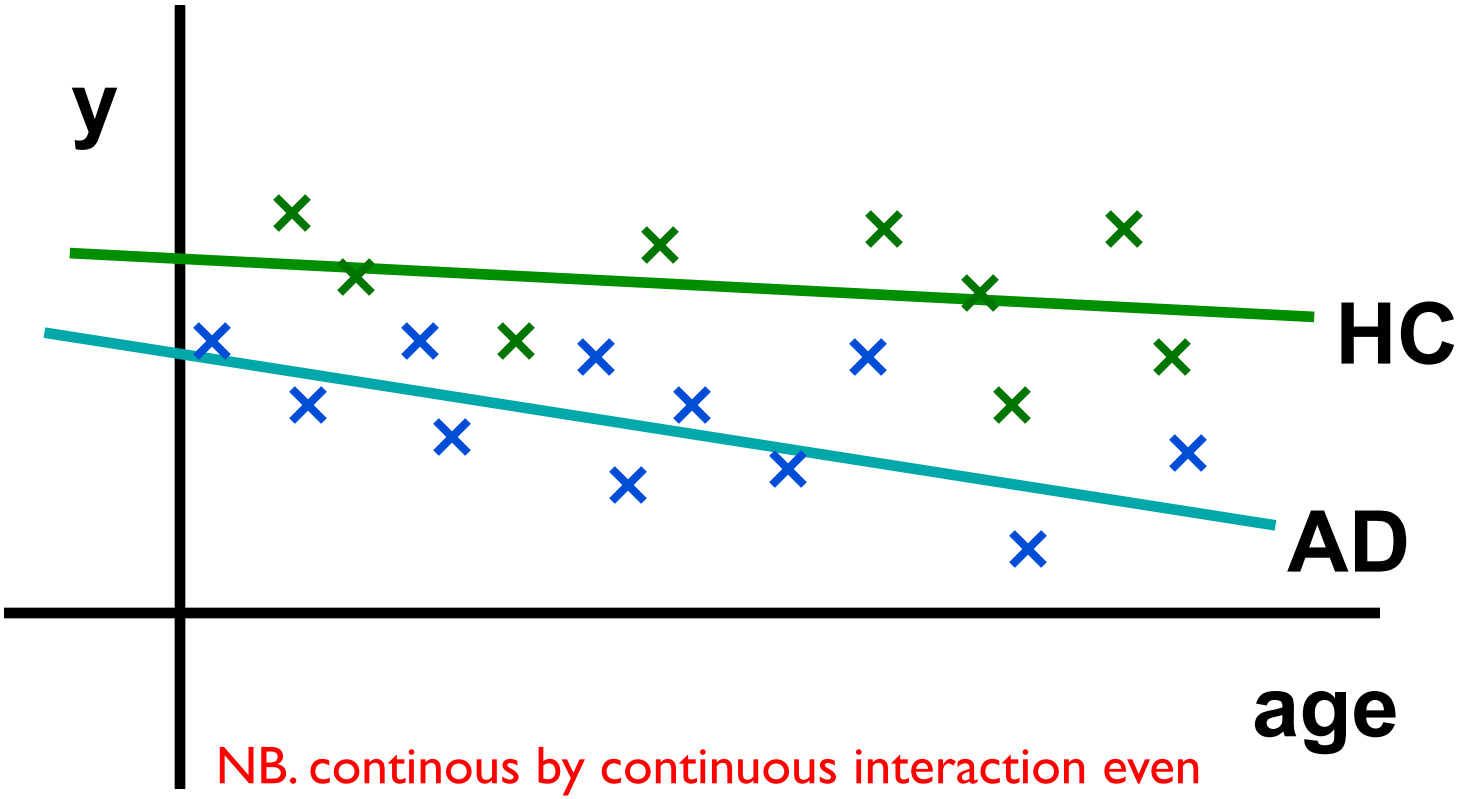
y = cognition score - outcome

$Dx = 1$, AD (Alzheimer's)

$Dx = 0$, HC (Healthy Control)

Case 4

$$\beta_{age} \neq 0, \beta_{Dx} \neq 0, \beta_{inter} \neq 0$$



NB. continous by continuous interaction even trickier to interpret – we won't go there

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]
-------------+----------------------------------------------------------------
    2.prevtx |   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|
           2 |   .9367223   .0153842    -3.98   0.000     .9070499    .9673652
------------------------------------------------------------------------------
```

What gives?

- There is a huge HR for `prevtx`.
  Is this an example of colinearity?

What gives?

- There is a huge HR for `prevtx`.
  Is this an example of colinearity?
- There might be some colinearity, but it is a minor issue here
- The big 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!

HR Interpretation

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
2.prevtx	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 | 2	.9367223	.0153842	-3.98	0.000	.9070499	.9673652

- `2.prevtx`: HR of previous transplant in year 0
- `year`: HR "year of tx" with no prev tx
  effect of +1 year when `prevtx=1` (ref group)
- `prevtx#c.year 2`: 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 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

	2.prevtx	year	product= 2.prevtx#c .year
previous transp.	1	1990	1990
no prev tx	0	1990	0
diff	1	0	1990

```
lincom 2.prevtx + 1990* 2.prevtx#c.year, hr
```

lincom

Effect of Previous transplant in 1990

```
. lincom 2.prevtx  + 1990* 2.prevtx#c.year, 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 2.prevtx  + 1995* 2.prevtx#c.year, 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 2.prevtx  + 2000* 2.prevtx#c.year, 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.

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]
-------------+----------------------------------------------------------------
    2.prevtx |   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 |
           2 |   .9367223   .0153842    -3.98   0.000     .9070499    .9673652
------------------------------------------------------------------------------
```

Only `2.prevtx` has changed: corresponds to effect of prev transplant in 1995

Effect of Previous Transplant in 1990

	2.prevtx	year	product= 2.prevtx#c .cyear
previous transp.	1	-5	-5
no prev tx	0	-5	0
diff	1	0	-5

```
lincom 2.prevtx  - 5 * 2.prevtx#c.cyear, hr
```

lincom (centered)

Effect of Previous transplant in 1990

```
. lincom 2.prevtx  - 5 * 2.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 2.prevtx  + 0 * 2.prevtx#c.cyear, hr
```

Effect of Previous transplant in 2000

```
. lincom 2.prevtx  + 5 * 2.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
------------------------------------------------------------------------------
```

Interaction

- Same advice as in linear and logistic regression models: *create product, test product, calculate lincom*
- Colinearity is not the problem
- 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

Summary of this lecture…

- Wald and likelihood ratio tests
- Zero/infinite HR
- Confounding, mediation, adjusting for other variables
- Interactions and `lincom` statements (danger of extrapolation)

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 4/14/15
- Lab 2 (available on syllabus page) session on Thursday MH 1400
- Reading for next lecture VGSM 6.3 - 6.5