Biost 518
Applied Biostatistics II

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Lecture 9:
Multiple Regression:
Modeling Dose - Response

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Lecture Outline

- Comparing statistical models
- Modeling complex “dose response”
- Flexible methods

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Comparing Models

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Hierarchical Models

- When testing for associations, we are implicitly comparing two models
  - “Full” model
    - Usually corresponds to the alternative hypothesis
    - Contains all terms in the “restricted” model plus some terms being tested for inclusion
  - “Restricted” model
    - Usually corresponds to the null hypothesis
    - Terms in the model are the subset of the terms in the full model that are not being tested

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Scientific Interpretation

- The scientific interpretation of our statistical tests depends on the meaning of the restricted model compared to the full model
  - What associations are possible with the full model that are not possible with the restricted model?

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Example: Adjusted Effects

- Hierarchical models:
  - Full model: FEV vs smoking, age, height
  - Restricted model: FEV vs age, height
- If the full model provides no advantage over the restricted model, we conclude that there is insufficient evidence to suggest an association between FEV and smoking

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Example: Tests of Linearity

- Hierarchical models:
  - Full model: Survival vs cholest, cholest^2
  - Restricted model: Survival vs cholesterol
- If the full model provides no advantage over the restricted model, we conclude that there is insufficient evidence to suggest a U shaped trend in survival with cholesterol

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Models with Interactions

- Best scientific approach:
  - Pre-specify the statistical model that will be used for analysis
- Sometimes we choose a relatively large model including interactions
  - Allows us to address more questions
    - E.g., effect modification
  - Sometimes allows greater precision
    - Tradeoffs between more parameters to estimate versus smaller within group variability

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Which Parameters Do We Test?

- It can be difficult to decide the statistical test that corresponds to specific scientific questions
  - Need to consider the restricted model that corresponds to your null hypothesis
    - Which parameters need to be set to zero?

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Ex: Full Model w/ Interactions

- Full model:
  - Survival vs sex, smoking, sex-smoking interaction
- Question:
  - Is there effect modification?
- Restricted model:
  - Survival vs sex, smoking
    - Test that parameter for sex-smoking interaction is zero

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Ex: Full Model w/ Interactions

- Full model:
  - Survival vs sex, smoking, sex-smoking interaction
- Question:
  - Association between survival and sex?
- Restricted model:
  - Survival vs smoking
    - Test that parameters for sex, sex-smoking interaction are zero

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Ex: Full Model w/ Interactions

- Full model:
  - Survival vs sex, smoking, sex-smoking interaction
- Question:
  - Association between survival and smoking?
- Restricted model:
  - Survival vs sex
    - Test that parameters for smoking, sex-smoking interaction are zero

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Why Not Pre-Testing

- We are often tempted to remove parameters that are not statistically significant before proceeding to other tests
  - Such data-driven analyses tend to suggest that failure to reject the null means equivalence
    - They do not
  - Such a procedure will tend to underestimate the true standard error
    - Multiple testing problems

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Interpreting "Negative" Studies

- "Differential diagnosis" of reasons for not rejecting null hypothesis of zero slope
  - There may be no association
  - There may be an association but not in the parameter considered (i.e, the mean response)
  - There may be an association in the parameter considered, but the best fitting line has a zero slope (a curvilinear association in the parameter)
  - There may be a first order trend in the parameter, but we lacked statistical precision to be confident that it truly exists (type II error)

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Interpreting "Positive" Results

- If slope is statistically significant different from 0 using robust SE
  - Observed data is atypical of a setting with no linear trend in mean response across groups
  - Data suggests evidence of a trend toward larger (smaller) means in groups having larger values of the predictor
  - (To the extent the data appears linear, estimates of the group means will be reliable)

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Modeling Complex "Dose-Response"

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Linear Predictors

- The most commonly used regression models use "linear predictors"
  - "Linear" refers to linear in the parameters
  - The modeled predictors can be transformations of the scientific measurements
    - Examples

$$g\left[\theta \,\middle|\, X_i, W_i\right] = \beta_0 + \beta_{\log X} \times \log\left(X_i\right)$$

$$g\left[\theta \,\middle|\, X_i, W_i\right] = \beta_0 + \beta_X \times X_i + \beta_{X^2} \times X_i^2$$

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Transformations of Predictors

- We transform predictors to provide more flexible description of complex associations between the response and some scientific measure
  - Threshold effects
  - Exponentially increasing effects
  - U-shaped functions
  - S-shaped functions
  - etc.

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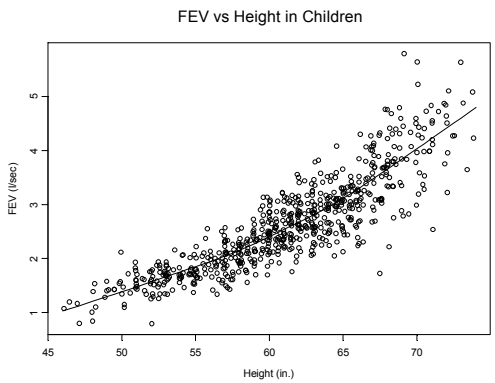
Ex: Cubic Relationship



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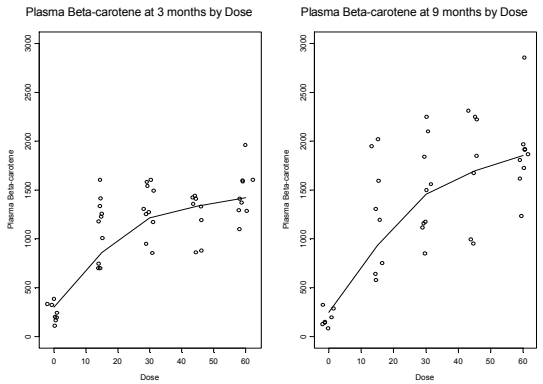
Ex: Threshold Effect of Dose?



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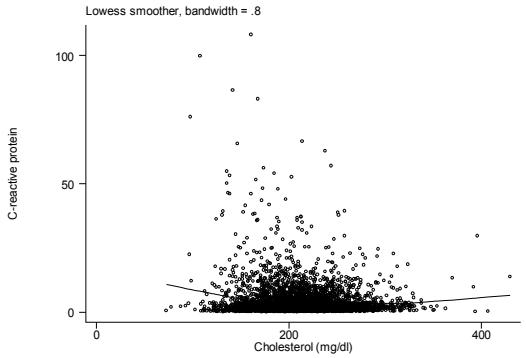
Ex: U-shaped Trend?

- Inflammatory marker vs cholesterol



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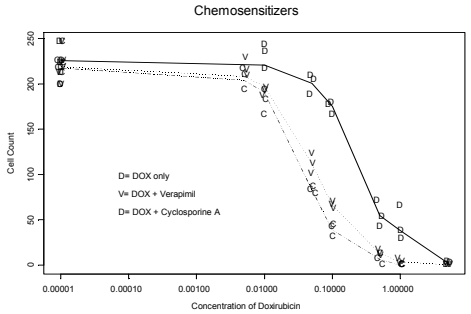
Ex: S-shaped trend

- *In vitro* cytotoxic effect of Doxorubicin with chemosensitizers



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"1:1 Transformations"

- Sometimes we transform 1 scientific measurement into 1 modeled predictor
  - Ex: log transformation will sometimes address apparent "threshold effects"
  - Ex: cubing height produces more linear association with FEV

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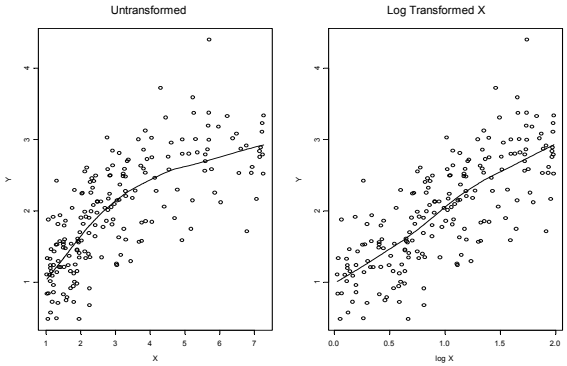
Log Transformations



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"1:Many Transformations"

- Sometimes we transform 1 scientific measurement into several modeled predictor
  - Ex: "polynomial regression"
  - Ex: "dummy variables" ("factored variables")
  - Ex: "piecewise linear"
  - Ex: "splines"

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Polynomial Regression

- Fit linear term plus higher order terms (squared, cubic, …)
  - Can fit arbitrarily complex functions
    - An n-th order polynomial can fit n+1 points exactly
  - Generally very difficult to interpret parameters
    - I usually graph function when I want an interpretation
  - Special uses
    - 2nd order (quadratic) model to look for U-shaped trend
    - Test for linearity by testing that all higher order terms have parameters equal to zero

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Ex: FEV – Height Assoc Linear?

- We can try to assess whether any association between mean FEV and height follows a straight line association
  - I fit a 3rd order (cubic) polynomial due to the known scientific relationship between volume and height

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Ex: FEV – Height Assoc Linear?

```
. g htsqr= height^2
. g htcub = height^3
. regress fev height htsqr htcub, robust
Linear regression                      Number of obs =     654
                                       Prob > F      =  0.0000
                                       R-squared     =  0.7742
                                       Root MSE      =  .41299
------------------------------------------------------------------------
             |       Robust
         fev |  Coef   SE      t   P>|t|     [95% C I]
------------------------------------------------------------------------
      height |  .0306 .635   0.05 0.962 -1.22   1.28
       htsqr | -.0015 .0108 -0.14 0.888 -.0227  .0196
       htcub | .00003 .00006 0.43 0.671 -.00009 .0001
       _cons |  .457  12.4   0.04 0.971 -23.8   24.76
```

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Ex: FEV – Height Assoc Linear?

- Note that the P values for each term were not significant
  - But these are addressing irrelevant questions:
    - After adjusting for 2nd and 3rd order relationships, is the linear term important?
    - After adjusting for linear and 3rd order relationships, is the squared term important?
    - After adjusting for linear and 2nd order relationships, is the cubed term important
  - We need to test 2nd and 3rd order terms simultaneously

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Ex: FEV – Height Assoc Linear?

```
. test htsqr htcub

 ( 1)  htsqr = 0
 ( 2)  htcub = 0

       F(  2,   650) =   30.45
            Prob > F =    0.0000
```

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Ex: FEV – Height Assoc Linear?

- We find clear evidence that the trend in mean FEV versus height is nonlinear
  - (Had we seen P > 0.05, we could not be sure it was linear– it could have been nonlinear in a way that a cubic polynomial could not detect)

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Ex: log FEV – Ht Assoc Linear?

- We can try to assess whether any association between mean log FEV and height follows a straight line association
  - I again fit a 3rd order (cubic) polynomial, but don't really have a good reason to do this rather than some other polynomial

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Ex: log FEV – Ht Assoc Linear?

```
. g logfev = log(fev)
. regress logfev height htsqr htcub, robust
Linear regression          Number of obs =     654
                           F(  3,   650) =  730.53
                           Prob > F      =  0.0000
                           R-squared     =  0.7958
                           Root MSE      =  .15094
       |        Robust
logfev |   Coef   SE     t   P>|t|  [95% C I]
height |  .0707 .24835  0.28 0.776 -.417   .558
 htsqr | -.0002 .00410 -0.04 0.964 -.0082  .008
 htcub | 3e-07  .00002  0.01 0.989 -.00004 .00004
 _cons | -2.79  4.985  -0.56 0.576 -12.6    6.997
```

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Ex: log FEV – Ht Assoc Linear?

- Note that again that the P values for each term were not significant
  - But these are addressing irrelevant questions:
  - We need to test 2nd and 3rd order terms simultaneously

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Ex: log FEV – Ht Assoc Linear?

```
. test htsqr htcub

 ( 1)  htsqr = 0
 ( 2)  htcub = 0

       F(  2,   650) =    0.29
            Prob > F =    0.7464
```

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Ex: log FEV – Ht Assoc Linear?

- We do not find clear evidence that the trend in mean FEV versus height is nonlinear
  - This does not prove linearity, because it could have been nonlinear in a way that a cubic polynomial could not detect
    - (But I would think that the cubic would have picked up most patterns of nonlinearity likely to occur in this setting)

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Ex: log FEV – Ht Assoc Linear?

- We have not addressed the question of whether log FEV is associated with height
  - This question could have been addressed in the cubic model by
    - Testing all three height-derived variables simultaneously
    - OR (because only height-derived variables are included in the model) looking at the overall F test
  - Alternatively, fit a model with only the height
    - But generally bad to go fishing for models

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Ex: log FEV – Ht Assoc?

```
. regress logfev height, robust
Linear regression                      Number of obs =     654
                                       F(  1,   652) = 2155.08
                                       Prob > F      =  0.0000
                                       R-squared     =  0.7956
                                       Root MSE      =  .15078
------------------------------------------------------------------------
       |               Robust
logfev |  Coef StdErr    t    P>|t|     [95% CI]
height | .0521 .0011  46.42 0.000   .0499    .0543
 _cons | -2.27 .0686 -33.13 0.000   -2.406  -2.137
```

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Dummy Variables

- Indicator variables for all but one group
  - This is the only appropriate way to model nominal (unordered) variables
    - E.g., for marital status
      - Indicator variables for
        - » married (married = 1, everything else = 0)
        - » widowed (widowed = 1, everything else = 0)
        - » divorced (divorced = 1, everything else = 0)
        - » (single would then be the intercept)
  - Often used for other settings as well
  - Equivalent to "Analysis of Variance (ANOVA)"

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Ex: Mean Salary by Field

- Field is a nominal variable, so we must use dummy variables
  - I decide to use "Other" as a reference group, so generate new indicator variables for Fine Arts and Professional fields

```
. g arts= 0
. replace arts=1 if field==1
(2840 real changes made)
. g prof= 0
. replace prof=1 if field==3
(3809 real changes made)
```

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Ex: Mean Salary by Field

```
. regress salary arts prof if year==95, robust
Linear regression                      Number of obs =    1597
                                       F(  2,  1594) =  120.85
                                       Prob > F      =  0.0000
                                       R-squared     =  0.1021
                                       Root MSE      =  1931.2
------------------------------------------------------------------------
             |       Robust
      salary |  Coef   SE      t    P>|t|     [95% CI]
-------------+----------------------------------------------------------
        arts | -1014   105   -9.67  0.000   -1219   -808
        prof |  1225   134    9.16  0.000     963   1487
       _cons |  6292   61.1  103.03  0.000    6172   6411
```

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Ex: Interpretation of Intercept

- Based on coding used
  - Intercept corresponds to mean salary for faculty in “Other” fields
    - These faculty will have arts==0 and prof==0
  - Estimated mean salary is $6,292 / month
  - 95% CI: $6,172 to $6,411 / month
  - Highly statistically different from $0 / month

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Ex: Interpretation of Slopes

- Based on coding used
  - Slope for “arts” is difference in mean salary between “Fine Arts” and “Other” fields
    - Fine arts faculty will have arts==1 and prof==0; “Other” fields wil have arts==0 and prof==0
  - Estimated difference in mean monthly salary is $1,014 lower for fine arts
  - 95% CI: $808 to $1,219 / month lower
  - Highly statistically different from $0

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Ex: Interpretation of Slopes

- Based on coding used
  - Slope for “prof” is difference in mean salary between “Professional” and “Other” fields
    - Professional faculty will have arts==0 and prof==1; “Other” fields wil have arts==0 and prof==0
  - Estimated difference in mean monthly salary is $1,225 higher for professional
  - 95% CI: $963 to $1,487 / month higher
  - Highly statistically different from $0

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Ex: Descriptive Statistics

- Because we modeled the three groups with two predictors plus intercept, the estimates agree exactly with sample means

```
. table field if year==95, co(mean salary)

    field | mean(salary)
     Arts |     5278.082
    Other |     6291.638
     Prof |     7516.67
```

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Stata: "Predicted Values"

- After computing a regression model, Stata will provide "predicted values" for each case
  - Covariates times regression parameter estimates for each case
  - "**predict *varname***"

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Ex: Salary by Field

```
. predict fit
(option xb assumed; fitted values)
. bysort field: summ fit
-> field = Arts
Vrbl |  Obs     Mean    SD       Min        Max
 fit |  220  5278.082   0   5278.082   5278.082
-> field = Other
Vrbl |  Obs     Mean    SD       Min        Max
 fit | 1067  6291.638   0   6291.638   6291.638
-> field = Prof
Vrbl |  Obs     Mean    SD       Min        Max
 fit |  310  7516.67    0   7516.67    7516.67
```

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Ex: Hypothesis Test

- To test for different mean salaries by field
  - We have modeled field with two variables
    - Both slopes would have to be zero for there to be no association between field and mean salary
  - Simultaneous test of the two slopes
    - We can use the Stata "test" command

```
. test arts prof
          F(  2,  1594) =  120.85
          Prob > F =    0.0000
```

    - OR because only field variables are in the model, we can use the overall F test

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Stata: Dummy Variables

- Stata has a facility to automatically create dummy variables
  - Prefix regression commands with "`xi: …`"
  - Prefix variables to be modeled as dummy variables with "`i.`*`varname`*"
  - (Stata will drop the lowest category)

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Stata: Dummy Variables

```
. xi: regress salary i.field if year==95, robust
i.field _Ifield_1-3(ntrlly coded; _Ifield_1 omitted)
Linear regression                      Number of obs =    1597
                                       F(  2,  1594) =  120.85
                                       Prob > F      =  0.0000
                                       R-squared     =  0.1021
                                       Root MSE      =  1931.2
------------------------------------------------------------------------------
             |      Robust
      salary | Coef   SE     t    P>|t|     [95% C I]
-------------+----------------------------------------------------------------
   _Ifield_2 | 1014 105    9.67 0.000   808     1219
   _Ifield_3 | 2239 146   15.30 0.000 1952     2526
       _cons | 5278 85.2 61.94 0.000 5111     5445
```

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Ex: Correspondence

- This regression model is the exact same as the one in which I modeled "arts" and "prof"
  - Merely "parameterized" (coded) differently
- Two models are equivalent if they lead to the exact same estimated parameters
  - Inference about corresponding parameters will be the same no matter how it is parameterized

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Continuous Variables

- We can also use dummy variables to represent continuous variables
  - Continuous variables measured at discrete levels
    - E.g., dose in an interventional experiment
  - Continuous variables divided into categories

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Relative Advantages

- Dummy variables fits groups exactly
  - If no other predictors in the model, parameter estimates correspond exactly with descriptive statistics
- With continuous variables, dummy variables assume a “step function” is true
- Modeling with dummy variables ignores order of predictor of interest

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Flexible Methods

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Flexible Modeling of Predictors

- We do have methods that can fit a wide variety of curve shapes
  - Dummy variables
    - A step function with tiny steps
  - Polynomials
    - If high degree: allows many patterns of curvature
  - Splines
    - Piecewise linear or piecewise polynomial
  - Fractional polynomial

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Stata: Linear Splines

- Stata will make variable that will fit piecewise linear curves
  - Joined at “knots”
  - Lines in between
- **`mkspline` *`newvar0 #k1 newvar1 #k2 newvar2 … #kp varp= oldvar`***
  - Regression on *newvar0 … newvarp*
    - Straight lines between min and k1; k1 and k2, etc.

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Ex: Height vs Age in Children

```
. mkspline  age6A 9.5 age12A   15.5 age17A=age

. regress height age6A age12A age17A
height |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
 age6A |   2.488554   .0999399    24.90   0.000     2.292311    2.684798
age12A |   1.085214    .088609    12.25   0.000     .9112196    1.259209
age17A |  -.5530841   .3713509    -1.49   0.137    -1.282276     .176108
 _cons |   38.49107   .8131791    47.33   0.000      36.8943    40.08785

. predict fitA

. sort age
. twoway (scatter height age, jitter(3)) (line fitA
  age)
```

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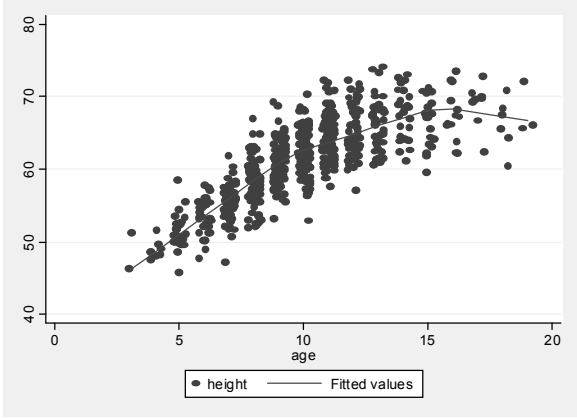
Ex: Height vs Age: 2 Knots



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Ex: Height vs Age: 4 Knots

```
. mkspline age4 6.5 age8 9.5 age11  12.5 age14 15.5
  age17=age

. regress height age4 age8 age11 age14 age17


. predict fit

. sort age

. twoway (scatter height age, jitter(3)) (line fit
  age)
```

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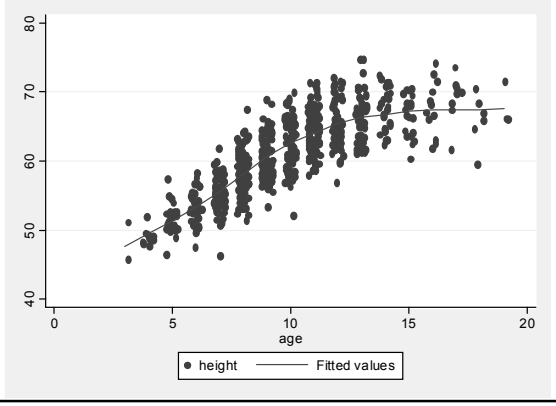
Ex: Height vs Age: 4 Knots



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Stata: fracpoly

- Stata will make variables modeling "fractional polynomials"
  - Can fit many different shapes depending on degree of the fractional polynomials
  - Can ask Stata to find "best" degree of the fractional polynomials: "`fracpoly`"
  - Can ask Stata to make new variables to model fractional polynomial of desired degree: "`fracgen`"

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fracpoly

- Command

fracpoly *regressioncommand yvar xvar*, degree(*#*)

Example

fracpoly regression logslry yrdeg, degree(*3*)

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Ex: 3rd Degree fracpoly

```
-> gen double Iyrde__1 = X^3-374.9107994 if
   e(sample)
-> gen double Iyrde__2 = X^3*ln(X)-740.6597949 if
   e(sample)
-> gen double Iyrde__3 = X^3*ln(X)^2-1463.219871 if
   e(sample)
    (where: X = yrdeg/10)

(Regression output omitted)

Deviance: 21329.66.
Best powers of yrdeg among 164 models fit: 3 3 3.
```

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Adjusting for Confounding

```
. regress logslry female Iyrde__1 Iyrde__2 Iyrde__3,
  robust
         |                Robust
 logslry |   Coef   SE      t    P>|t|     [95% C I]
  female |  -.119 .007  -16.87 0.000  -.133   -.106
Iyrde__1 |  -.111 .014   -7.68 0.000  -.139   -.082
Iyrde__2 |   .088 .012    7.30 0.000   .065    .112
Iyrde__3 |  -.018 .003   -6.91 0.000  -.023   -.013
   _cons |   8.36 .004 1983.98 0.000  8.35    8.36
```

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